The Role of The Locus Coeruleus Noradrenergic System in Tracking the Statistics of Rapid Sound Sequences

Sijia Zhao

Supervised by:

Professor Maria Chait

Professor Frederic Dick

A thesis submitted in partial fulfilment for the degree of Doctor of Philosophy

At the Ear Institute, Faculty of Brain Sciences, University College London, UK

April 2018

物之生也，若骤若驰，无动而不变，无时而不移。
何为乎？何不为乎？夫固将自化。

—— 庄子《秋水》

The world of things is like the hurrying and galloping of a horse. With every movement, there is a change; with every moment, an alteration. What should you be doing? What should you not be doing? Just allow the course of natural transformation to go on.

—— Zhuangzi, *Autumn Floods*

Declaration

I, Sijia Zhao, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis. It has not been previously submitted, in part or whole, to any university or institution for any degree, diploma or other qualification.

By the University College London guidelines, this thesis does not exceed 100,000 words, and it contains less than 150 figures.

Signature:

Date:

Sijia Zhao

London, UK

5th February 2018

Abstract

The sensory world is full of uncertainty; most perception-relevant statistics are highly dynamic, featuring frequently-changing patterns. Rapid adaptation to the everchanging world requires brain sensitivity to environmental changes and resetting of functional neural networks as needed. Norepinephrine (NE) is proposed to mediate this process by initiating functional resetting (Dayan and Yu, 2006; Sara and Bouret, 2012) via the Locus Coeruleus (LC)-NE system. This doctoral thesis employs pupil diameter measurements – a reliable indicator of NE neural activity in the LC (Aston-Jones and Cohen, 2005; Joshi et al. 2016).

Human participants listened to sequences of adjoined 50ms tone-pips (adapted from Barascud et al., 2016) containing transitions from random to regular frequency patterns and vice-versa. Participants were instructed to detect occasionally inserted silent gaps, ensuring attention to the auditory stream, not the transition itself. Although both transitions (regular-to-random and random-to-regular) are clearly detectable behaviourally and evoke strong MEG (Barascud et al., 2016), only violations of regularity (prediction errors) appear to elicit pupil responses. Noteworthily, this response is driven by pattern changes and not merely deviant detection.

However, stimuli containing pattern emergences (precision increase) evoke no measurable pupil response; this is not due to pre-transition pupillary saturation, as transitions from random patterns to repeating single tones (random-to-repeating) evoke transient pupil dilation. Only when subjects actively reported changes in button-press did random-to-regular transitions evoke pupil dilations.

Investigating the effect of task on evoked pupil responses found no response if subjects were not continuously tracking the sequences, e.g. with attention directed to visual or tactile stimuli.

Multiple self-replications of these findings provide robust evidence that NE release acts as an automatic switch, resetting the brain's internal model of the sensory environment and demonstrating that the unexpected uncertainty signalling process operates over much faster timescales than previously known, implicating NE in the fundamental bases of perception.

Impact Statement

The surrounding world is full of uncertainty and rapidly changes from one state to another. In order to make sense of what is happening, we need to constantly update our understanding of the world and remain alert to changes that occur. A major scientific mystery is how our brains keep updated and remain alert to these changes. By using the eye as a window into the brain, we discovered that norepinephrine (NE) – a neuromodulator associated with arousal and the fight-or-flight response – may play a key role in this process. More specifically, we found that people's pupil dilation - an index of norepinephrine modulation - is selectively sensitive to violations of both predictable and random sound patterns. This finding provides strong evidence that NE signals a form of surprise and may act as a 'resetting switch' in the brain to interrupt existing internal models of the world, and to promote learning about ‘what’s new’ in our surroundings. This finding contributes to the theoretical framework on how the brain processes highly dynamic sensory information over time.

In addition to providing confirmatory evidence for the existing theory, this doctoral thesis also introduced a brand-new, simple and very flexible experimental paradigm to investigate the NE neuromodulator system in humans. The NE system has been implicated in many psychiatric and neurodegenerative disorders, including Parkinson’s and Alzheimer’s diseases, and Autism Spectrum Disorder. Therefore, identifying the processes that detect and communicate changes in the external environment, along with the specific role of the NE system in these processes, would be invaluable for both clinical diagnosis and scientific exploration.

Previous literature has consistently found pupil diameter to be strongly correlated with neural activity in the locus coeruleus, the brainstem region responsible for NE generation in the entire brain. Here, we probed the activation of the NE system via the measurement of pupil diameter (pupillometry), demonstrating the robustness and convenience of this method, making it a very attractive and non-invasive means to study NE in human brain. This provides

inspiration for exploring the neuromodulator system and facilitates the transfer of knowledge from animal models to humans.

Beyond its benefits to the field of neuromodulator study, this thesis also developed a new single-trial-based analysis which provides a new perspective on pupillometry data, raising the possibility of revisiting previously collected data. Chapter 2 of this thesis includes a guide on both pre-existing and novel pupillometry analysis methods; this is helpful for anyone who is interested using pupillometry as a tool for cognition, from beginner to experienced.

Acknowledgements

First and foremost, I want to thank my primary supervisor (academic mother) Professor Maria Chait, who provided me many precious opportunities and constant support during my PhD and acted as a role model to me not only academically but also in life. There are many things Maria has taught me, but nothing was more precious than her enthusiasm to push the boundaries of human knowledge. If not for her dedication, motivation and energy, this study and many others not covered in this thesis would undoubtedly never have achieved fruition.

A similar gratitude belongs to my secondary supervisor (academic father) Professor Frederic (Fred) Dick, who has supervised me since I was an undergraduate in BSc Neuroscience at UCL. He and Professor David McAlpine nurtured my passion for auditory neuroscience and encouraged me to embark on the path of cognitive neuroscience.

Maria and Fred have often made me feel privileged to be their PhD student. They have shown me, both consciously and unconsciously, how exemplary cognitive neuroscience should be carried out. Their work ethic taught me not to settle for mediocrity, which has deeply changed the way I think and live.

I would also like to thank my pupillometry *Senseis* Dr Shigeto Furukawa, Dr Hsin-I Liao and Mr Makoto Yoneya, for sharing their pupillometry expertise and providing precious advice on the experimental design. In fact, it was Hsin-I who first suggested and kickstarted the preliminary work for this thesis. Makoto also taught me volumes of knowledge and techniques during another series of pupillometric work not covered by this thesis. I also want to thank them for looking after me with such kindness and patience at the NTT Communication Science Laboratories, Atsugi, Japan in the autumn of 2016, and for taking me to try so many different restaurants. I would not have been able to complete this study (Experiment 6 of this thesis) in Japan without their help.

I also want to thank Dr Nicolas Barascud, my academic brother, who was, at the time I had just started my PhD, also Maria's PhD student. He developed the stimuli used in this thesis and his works have provided a solid foundation for my work. More importantly, at the beginning of my PhD, he helped me greatly in many aspects, from teaching me to develop good programming habits, and sharing his expertise in M/EEG analysis to introducing me to the research community at UCL.

I also want to thank all the members of the UCL Ear Institute that I have had the pleasure of working with, especially Daniel (for all the funny and not-so-funny jokes), Ulrich, Kate, Theo, Rosy, Mathilde, Ed, Cécile, Alice, Roberta, Alex,Yinuo, Lucas, Michelle, and Joseph who introduced me the beauty of gin and tonic which became a staple of my three-month thesis writing period. I also want to thank the staff at the Costa Coffee across the road for brewing me more than 900 cups of coffee in the last three years and bearing with my picky coffee habits.

I also must say thank you to my lovely (mostly Chinese) subjects (over 600 in total). They were extremely patient and kind (some even bought me coffee and cake for encouragement). Many of them showed significant interests in neuroscience after attending my tedious experiments and even encouraged their friends to attend my study. Without their presence and participation, I would not have been so productive over last three years.

Of course, thanks must go to my parents. My parents do not speak English and have no idea what neuroscience is, but they tried their best to support and encourage me to do what I want. Without their constant support, I would never have had a chance to start and finish a PhD or even to come to study in London.

Finally, I want to thank my husband, Mark. There is so much I want to say but so little that can be expressed. He created a comfortable environment allowing me to focus on my work without any worries and housework in the last three (seven) years. Although he is not a neuroscientist, he is always the first to hear my presentations and read my drafts, followed by

stimulating discussions and patient English tutoring. Without his help and encouragement, it would have been impossible for me to go through the last three years without any regrets.

These were the happiest three years I have had. While challenging, it was undoubtedly exciting. Thank you to everyone I have met along the way.

Figure 0. My academic family. From left to right, my great-great grandpa, great-grandpa, grandpa, mum, dad, me and my older sister (four brothers and four sisters are not shown). Taken at the International Conference on the Auditory Cortex, Banff, Canada (September 2017).

Contents

List of Figures

1 General Introduction

Understanding how the brain makes sense of our sensory environment is a major challenge in neuroscience. It has been suggested that our brain perceives the world through inference; internal representations about the external world are constructed by predicting future behaviour based on preceding sensory inputs, and comparing these predictions with upcoming sensory input (Friston, 2005; Rao and Ballard, 1999).

However, as the surrounding world is highly dynamic and full of uncertainty, sensory signals continuously fluctuate and change over time. To rapidly adapt in such a dynamic world, the brain needs to continuously track rapidly changing statistics in the signal surrounding us. The term “statistics” as used here describes a range of metrics which can be extracted from the signal across its various dimensions, for example, time, space, and auditory frequency amongst others. If the actual sensory input is inconsistent with predictions – an indication of a critical change-point in the environment – then the brain must modify the weights of the internal model about the external world to maintain the model’s accuracy, reliability and relevance.

The locus coeruleus-norepinephrine (LC-NE) system has been hypothesised to play a critical role in this updating process (Bouret and Sara, 2005; Dayan and Yu, 2006; Yu and Dayan, 2005). Specifically, phasic noradrenergic activity in the LC is believed to mediate this process by initiating resetting or interrupting relevant functional neural networks to effectively adapt to the environment. However, as reviewed below, the majority of the previous literature focuses on the role of the LC-NE system in tracking slowly changing statistics, providing little clarity on how this process is affected by behaviour. For example, does the change detection of this system require the brain to actively look for the changes or is it independent of the

decision-making process? This doctoral thesis aims to address these questions by investigating the sensitivity of the LC-NE system to changes in structure within very rapid sound sequences. As pupil dynamics have been demonstrated to be a reliable indicator of the neuronal activities in the LC, pupillometry is used to measure the activity of the LC-NE system in human brains.

Before introducing the experimental results, this thesis opens with a review of theoretical and experimental studies covering how the brain is able to rapidly adapt to the ever-changing sensory world, and in particular, how the LC-NE system is proposed to be involved in this process. This is followed by a review of previous studies on this role of the LC-NE system, with a focus on the human pupillometric evidence for the role of the phasic NE response. As this thesis is based on the notion that pupillometry is a means of indirectly measuring the LC-NE activity, there is a particular focus on the relationship between pupillary responses and noradrenergic activity in the brain, with a review of its reliability and a detailed overview on pupillometry (Chapter 2 General Methodology, p61).

1.1 Perceiving through predictions

1.1.1 Analysis-by-synthesis

What is perception? For centuries, philosophers and cognitive scientists alike have posed, deconstructed and debated this question. Albert Bregman described the role of perception as a process “to take the sensory input and to derive a useful representation of reality from it” (Bregman, 1990). What has been clear is that deriving a representation from sensory information is not a passive process; sensory information does not simply flood into the brain. In fact, our brains may perceive the external world through continuous predictions, an idea first proposed by Helmholtz’s (1867) theory of unconscious inference or *unbewusster Schluss*, which explains visual perception as the result of unconscious inferences drawn from a combination of knowledge and prediction (Clark, 2013). Essentially, this describes how the

brain can predict missing or unobservable visual information to complete and interpret a scene. Helmholtz's work recounts the illusion of the sun rotating around the Earth: The sun appears to rise and traverse the sky overhead before setting and descending below the horizon, despite the common knowledge that the sun remains stationary relative to the Earth's rotation. In this case, the brain uses the relative motion of the sun against the apparently stationary horizon to infer the circular movement of the sun. From this, perception can be described as the result of the brain's best guess of how the surrounding world should have to behave in order to produce the sensory information received.

Importantly, this initial idea laid the foundations for the analysis-by-synthesis theory (Gregory, 1980; MacKay, 2003; Neisser, 1967; for review see Yuille and Kersten, 2006). This theory proposed that the brain does not perceive by building a bottom-up model of the world through aggregation of sensory cues, but rather starts from a top-down concept-driven internal model which predicts the most likely situations given the sensory input (Chater et al., 2006; Neisser, 1967; Yuille and Kersten, 2006)

The understanding of perception as the interaction between sensory stimuli and experience-based expectation was then further established by McClelland and Rumelhart (1981). In their seminal paper, participants were presented with processing features (lines and contours) forming letters, which in turn comprise words. McClelland and Rumelhart found that when letters form a word, participants were able to identify letters faster than when letters were situated in a non-word without semantic context, suggesting that letter perception is a meeting of bottom-up and top-down information.

This finding further inspired machine learning scientists. One such innovation was the "Helmholtz Machine" (Dayan et al., 1995; Dayan and Hinton, 1996; Hinton and Zemel, 1994), an early example of an artificial neural network that did not require the experimenter to classify training data in advance. Instead, it must first learn how to generate the incoming data for itself. An example of the application of this idea is a simple multilayer model described by Hinton and Salakhutdinov (2006) used to identify handwritten digits. The model contained three layers of

feature detectors trained on 60,000 unlabelled images of handwritten digits. Instead of starting to classify the images directly, the model learned a probabilistic generative model to produce such images for itself by "adjust[ing] the weights on the top-down connections so as to maximise the probability that the network would generate the training data" (Hinton, 2007a, p428). This model's performance on handwriting identification was impressive and exceeded all standard artificial neural networks (Hinton, 2007a, 2007b; Hinton and Salakhutdinov, 2006; Nair and Hinton, 2006). Predominantly, this simple machine learning model mastered this digit identification task in a way that mirrors that of the human brain, which also uses "the strategy of using top-down connections to try to generate, using world knowledge, a kind of virtual version of the sensory data via a deep multilevel cascade" (Clark, 2016, p. 25). It is this strategy that lies at the heart of hierarchical predictive coding to perception (Clark, 2016; Friston, 2005; Lee and Mumford, 2003; Rao and Ballard, 1999).

1.1.2 Predictive Coding

The concept and the name of predictive coding draw its inspiration from data compression for signal processing (Clark, 2016; see Shi and Sun, 2017 for a history of data compression predictive coding). In digital computer images, one unit – a pixel – often has a relationship with its neighbouring pixels and can be predicted if missing or corrupted. As a result, large images which would normally occupy a sizable amount of computer storage space can be compressed through examining the relationships and variations between the pixels themselves, and therefore storing the image as a smaller computer file codifying only the *unexpected* variations; in the context of neuroscience, these variations are prediction errors (reviewed in detail below).

In neuroscience, the apparent prevailing theory of perception is that the brain constructs an internal hierarchical generative model of the external sensory world. The predictive coding theory suggests that, to ensure that this model is representative of the external world, the brain continuously predicts the likelihoods of future sensory input and then

tests the predictions against the actual sensory input (Clark, 2016; Friston, 2005; Lee and Mumford, 2003; Rao and Ballard, 1999). This concept combines top-down probabilistic generative models which continuously produce predictions of the incoming sensory information. Any residual unpredicted elements – *prediction errors* – direct the flow of information through the system.

According to this theory, the brain is structured hierarchically, and perception is assumed to be a continuous process running concurrently across multiple levels of the neural processing hierarchy in the brain (Friston, 2005, 2008, 2010). The predictions generated on each level have different time scales – short-term and long-term predictions – that are assumed to increase along with hierarchical organisation in the cortex (Kiebel et al., 2009). Here, it is proposed that upper layers produce predictions and propagate these downwards, while lower layers relay observations of actual sensory input upwards (Bastos et al., 2012; Friston, 2005; Rao and Ballard, 1999); if the internal models are consistent with the sensory input, then each layer of neural processing is trying to predict the upcoming sensory information for the layer below itself and also receiving a feed-forward connection conveying the actual sensory information (Friston, 2010, 2005; see also Heilbron and Chait (2017) for a review on arrangements in the auditory cortex).

If a bottom-up message does not match the top-down prediction, this mismatch induces a prediction error. As such, prediction errors are placeholders for unpredicted and unexplained information, signalling the surprise triggered by the discrepancy between prediction and reality (Friston, 2005, 2010). At the same time, to minimise the prediction error, the brain needs to continuously update existing models or select new models to minimise the difference between its predictions about the sensory input and the actual sensory input in order to adapt the internal model to the external world.

If the predictive coding theory is correct, the brain's primary objective is to infer the underlying causes of the sensory input by evolving models to minimise surprise, with the objective of producing successful predictions to interact with the world. This provides a system

in which the sensory input is used as a form of feedback from reality. In other words, instead of considering the brain as a passive encoder of the world's state, predictive coding sees the brain as an active, predictive synthesiser which is supervised with feedback from sensory input. In this way, the processing overheads and workloads are much reduced as it avoids facsimileing the world with unnecessarily rich details but still manages to capture the potentially important differences between the prediction based on the preceding input and the actual ongoing sensory signal.

Precision

In this noisy ever-changing world, the balance between top-down and bottom-up influences must adjust dynamically depending on context. In some situations, like holding a conversation in a noisy pub, the sensory input is very much noise-dominated as much of the dialogue is masked by background noise – often to the extent of being completely drowned out – so detailed prior knowledge and contextual expectation greatly improve the interpretation of such input. In contrast, when listening to a single speaker in a quiet auditorium, the sensory input is clear and reliable thus it would be better to let the sensory input take the lead. Therefore, the context-varying reliability of the current sensory environment guides behaviour and moderates decisions to be more top-down expectation-driven or bottom-up input-driven. Under the framework of predictive coding, how would the brain handle this problem? Here, it would have to continuously estimate and re-estimate its own sensory uncertainty or confidence of the current sensory input and reprocess those estimations to modulate the impact of prediction error signals.

In other words, prediction errors are weighted by their reliability – quantified as the inverse variance of the sensory input. This measure of the estimated reliability is termed "precision"; greater precision signifies higher reliability, enhanced confidence and reduced uncertainty in the current sensory input and begets higher gain on the relevant error units (Feldman and Friston, 2010; Friston, 2005, 2010). According to Feldman and Friston (2010), if the sensory input is very precise (for example, a regularly repeating melody), any unexpected

signal would result in a heavily weighted prediction error, and the inference would be dominated by the bottom-up sensory information. In other words, when sensory input is highly predictable, predictions are very reliable. Hence any signal violating the prediction would be surprising and indicate a need to prioritise sensory input for further processing. On the other hand, if the sensory input is of low precision and high uncertainty (for example, a tone sequence with random frequencies) a prediction error should be down-weighted, and the inference would be dominated by top-down expectation. Ultimately, this means that the impact of a prediction error varies according to its precision. This precision weighting thus suggests that top-down predictions integrate information from both the content and the perceived confidence of lower-level presentations (Friston et al., 2012, p. 238).

This hypothesis has been used to explain attention under the predictive coding framework (Feldman and Friston, 2010). Attention is hypothesised to balance the top-down and bottom-up interaction by controlling synaptic gain on the neural units signalling prediction error, the prediction error units. More specifically, the degree of synaptic gain is proposed to have a positive correlation with the precision of sensory information. Neurologically, the optimisation of synaptic gain has been thought to be mediated by the cholinergic system (Yu and Dayan, 2005; see the following section for more discussion). The precision-weighting prediction theory and its implications for attention will be discussed subsequently.

1.1.3 Patterns in the world

Apophenia refers to the tendency to attribute meanings to meaningless noise, or say, finding meaningful patterns in meaningless noise. For example, the “man in the moon” phenomenon is the perception of a face on an inanimate object. This concept has been traditionally ascribed to an error in perception, but there are suggestions that this is a misattribution: Apophenia may not be a flaw in the human brain after all but reflects a universal human tendency to find patterns in sensory input.

As mentioned previously, the concept of predictive coding was successfully employed in the field of signal processing to store images more effectively by exploiting patterns in signals to create predictions and signal discrepancies as prediction errors. In some way, data compression is quite a fitting analogy for the world. Both are highly structured, with many levels of patterns across multiple dimensions. Patterns can be described as discernible regularities with elements repeating predictably. The word “pattern” originated from the French *patron*, which refers to “something serving as a model”. Meanwhile, the Chinese equivalent, 紋, can depict wood veins, silk threads or ripples, touching on the universality of patterns in nature and the human-made. This is especially evident in visual scenes which exhibit multiple levels of recursive elements; a natural scene like a forest is composed of trees, with trunks, branches, and leaves, while a human-made scene like a city contains buildings, with walls, windows and window panes.

Predictability in sounds

The ubiquity of patterns is also particularly evident in the auditory domain. The presence of predictable elements can be found across different dimensions (spectrum and time) and at all levels (e.g. across different time scales) of natural sounds (McDermott et al., 2009), and can be visualised with spectrograms (Figure 1.1). The frequency content and texture appear as coloured bands and some signature features – such as the crackles and pops of a fire – appear as bands traversing the spectrogram. Sounds generated for communication between animals normally have a temporal structure that carries critical information or a signature. One such example is the nocturnal calls made by insects which exhibit temporal regularity. In humans, instrumental music displays similar characteristics, with melodies composed of repeating and evolving sequences.

Animal vocalisations, especially human speech, are constructed from sequences of patterns exhibiting fluctuating degrees of variability, and thus can be decomposed into units with static or distributed relationships (Redington and Chater, 1997). For instance, upcoming words would be more predictable given a preceding context (e.g. see the review Elman, 2009),

which is particularly helpful when holding distorted conversations over crackly telephone lines or understanding speech in noisy situations where some words are completely masked. Due to the probabilistic nature of language, rarely is a spoken utterance completely unpredictable; most often, the next word in a sentence depends on the preceding context.

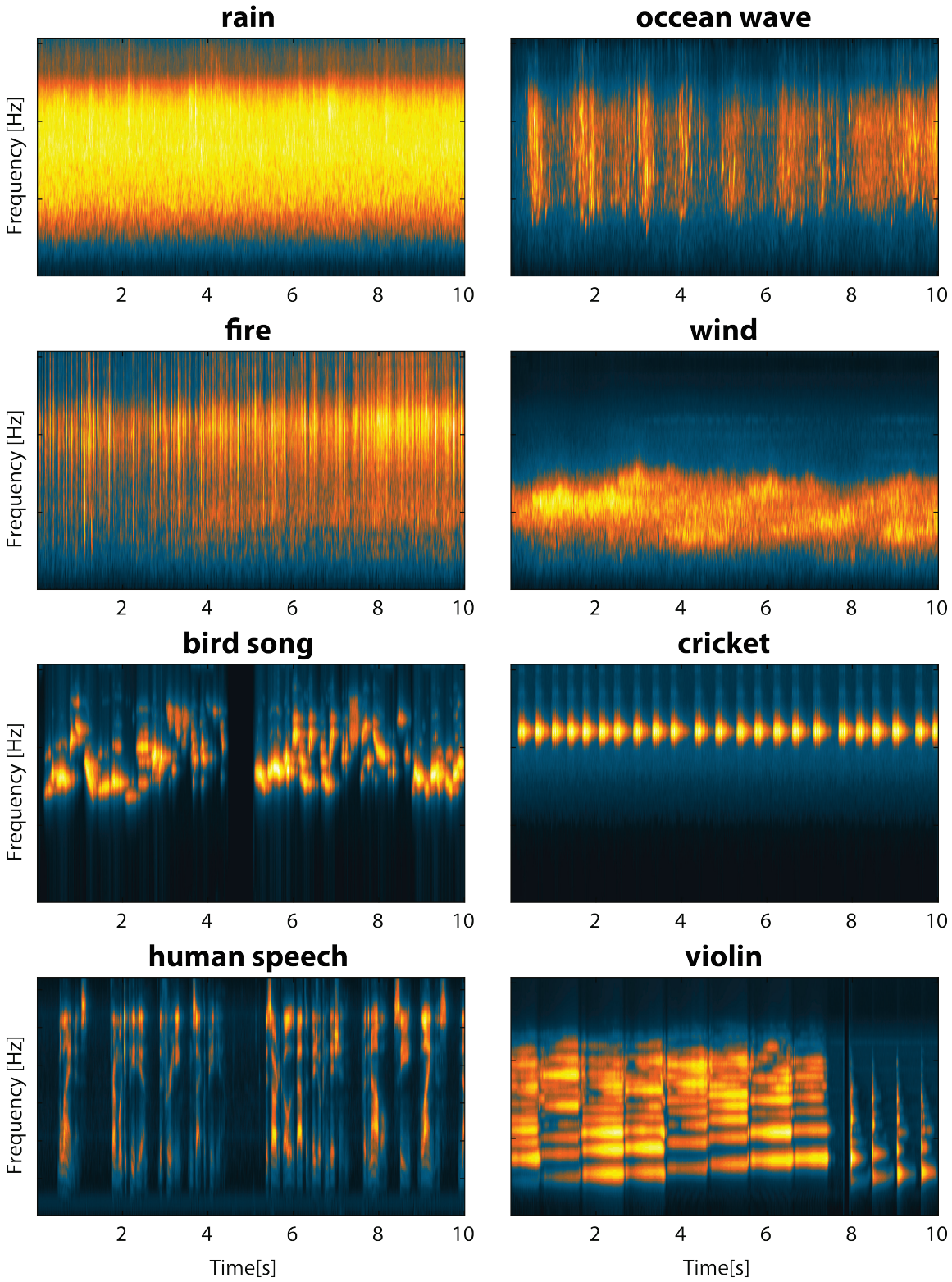


Figure 1.1 Spectrograms of examples of natural sounds. Sound examples were downloaded from www.zapsplat.com.

Sensitivity to the statistical structures in human language: Statistical learning

One rather fiting example that demonstrates the presence of predictable patterns in auditory input and the remarkable sensitivity of the brain to such patterns is human language. Spoken language is a continuous sequence of words. Typically, there is no clear boundary between words, thus raising the question of how infants manage to segment words and learn languages. Here, the statistical properties of language are particularly useful for word segmentation. Take a simple example in English, the two-word sequence *pretty baby*: In speech to young infants, the syllable ***pre-*** is followed by ***-tty*** with a high probability (80%, Saffran, 2003), while the probability that ***-tty*** is followed by ***ba-*** is extremely low (0.03%, Saffran, 2003). Hence, these are statistical cues which can be leveraged to designate word boundaries, and the ability to extract such statistical structures might be key to language acquisition.

In a seminal study (Saffran et al., 1996), 8-month-old infants listened to a continuous syllable stream consisting of four three-syllable "words" – sets of three syllables with a high probability in the stream (e.g. "golabu") – presented in a random order (e.g. ***golabu****pabikututibubabupu****golabu****…*) for 2 minutes. Even with this short exposure, infants could discriminate familiar words from non-words. In this artificial speech, the "words" are present but word boundaries unmarked. The only cues to word boundaries are the statistical properties of the syllable sequence. Thus, to succeed in this task, the infants must track the statistical properties of the syllables.

Further studies have shown that human adults, young children and infants are all capable of transitional computing probabilities among adjacent syllables in rapidly presented streams of speech, and of using these statistics to group syllables into word-like units (Fitch and Hauser, 2004; Hauser et al., 2001; Saffran et al., 2008; see more in a recent review Saffran and Kirkham, 2018). Moreover, this ability to learn the statistical structures in a continuous sequence, termed as statistical learning, is not purely a linguistic mechanism but widely available in sensory processing, for example, auditory pure tones (Saffran et al., 1999), visual

shapes (Fiser and Aslin, 2001, 2002a, 2002b, 2005; Kirkham et al., 2002; Turk-Browne et al., 2005, 2008) and even tactile stimuli (Conway et al., 2010). Moreover, by employing the Artificial Grammar Learning (Reber, 1967) paradigm, non-human animals, such as various types of monkeys (Fitch and Hauser, 2004; Hauser et al., 2001; Milne et al., 2017; Saffran et al., 2008; Wilson et al., 2013) have also demonstrated this striking ability to acquire statistical structures.

1.1.4 Evidence for predictive coding

By taking advantage of the fact that well-ordered and predictable elements pervade the surrounding world, predictions can spur learning and structural knowledge. Following this, the predictive coding paradigm envisages the brain as a predictive regularity detector, continuously capturing regularities within incoming signals and learning how future signals are most likely to behave. Therefore, the encoding of regularities is an essential task of predictive processes, constituting a cornerstone of perception (Clark, 2013; Friston, 2005; Hohwy, 2013).

In audition, the concept of *regularity* describes “a repeating property of a sound sequence” (Winkler et al., 2009, p553). However, regularity is not limited to the simple repetitions of sound, or deterministic rules like “short tones are followed by a low tone” (as in Paavilainen et al., 2007), but could also represent abstract relationships like transitional probability in statistical learning (e.g. Saffran et al., 1996, as reviewed in the previous session), and even more complex stochastic patterns (Barascud et al., 2016; detail will be reviewed later). It is thus unsurprising that regularity encoding has been extensively studied in the last two decades, serving well to highlight our remarkable ability to extract and represent patterns.

Although the precise neural mechanism of regularity encoding is yet unclear, the idea that the brain continuously and effortlessly extracts structures from the surrounding environment to predict future events has been widely accepted (Barascud et al., 2016; Denham and Winkler, 2006; Schröger et al., 2014; Winkler et al., 2009; see more in recent reviews, Denham and Winkler, 2017; Heilbron and Chait, 2017). Particularly, the predictive

coding framework has been found to explain possibly well the most well-studied neural signature of error processing, namely the mismatch negativity.

Mismatch negativity

Mismatch Negativity (MMN) is an electrophysiological brain response evoked by an unexpected event (Garrido et al., 2009; Näätänen et al., 1978, 2007; Schröger et al., 2007). A typical experiment presents participants with a series of frequently-occurring and expected stimuli ("standards"). Occasionally, an unexpected or oddball stimulus ("deviant") is presented, resulting in an evoked response that can be recorded non-invasively with electrophysiological techniques (e.g. EEG and MEG) as a component of the event-related potential. The MMN is a difference wave computed by subtracting the response to the standard stimulus from the response to the deviant stimulus, peaking at 100-250ms after the onset of the deviant, in the temporal and frontal areas of topographic scalp maps (Sams et al., 1985). Thus, the presence of MMN demonstrates the detection of violation of expectation and allows the indirect conclusion that the brain has extracted the corresponding information differing standard and deviant from the signal (Näätänen and Winkler, 1999; Schröger et al., 2007).

A brief review on regularities known to elicit the MMN

The unexpected event can be the occurrence of an unexpected stimulus which typically differs from the standards in their basic physical features, such as sound frequency, intensity or spatial localisation (for review see Näätänen et al., 2010, 2007). Moreover, the elicitation of the MMN is not limited to physical property violations of individual tones but encompasses violations in the relationships between tones, which was first shown by Saarinen et al. (1992). In that study, the regularity was manifested as a frequency relationship between pairs of tones; the standards were pairs of tones with ascending frequency, and the deviants with descending or constant frequency.

Additionally, the elicitation of the MMN can be extended to violations of more complex standards, for example, in Paavilainen et al. (2007) where one feature of a stimulus is defined by a different feature of a preceding stimulus. Paavilainen et al. presented a tone sequence

composed of either long or short duration tones which could be either high or low in frequency. The standard tones obeyed the relationship “long tones are followed by high tones, and short tones are followed by low tones”, while deviant tones were randomly inserted to violate this.

As with most of the studies in the field, this paradigm can indicate whether the rule (like “long tones are followed by high tones”) has been extracted by the listeners. However, a shortcoming exists in that only one rule features in experimental blocks (Bendixen et al., 2008), and thus the process of learning the regularities itself cannot be captured. In a later study, Bendixen et al. (2008) employed a dynamic experimental paradigm where multiple rules were used. As in the previous experiment, the stimulus started with a sequence of standard tones following a rule (Rule A). Later, this rule was violated by inserting a random sequence of tones. After a while, the stimulus became a sequence of standards tones following an unpredictable rule; this could either be the original rule (Rule A), or a different novel rule like Rule B. This paradigm is called the roving-standard approach (Cowan et al., 1993) and models a dynamic situation where rules continuously emerge and vanish (Bendixen et al., 2007). Even with this more complex stimulus, the MMN response was still observed in EEG recording, despite participants being unaware of the presence of regularities.

Furthermore, a few studies have introduced degrees of variability into the distribution of standards, for example, intensity (Winkler et al., 1990), tone duration (Cheng et al., 2010) and frequency (Garrido et al., 2013); the given feature was varied within a certain range, and whenever a deviant with a feature outside of this range was presented, an MMN response was observed. Garrido et al. (2013) used a stochastic sequence of pure tones where the frequencies of the tones were selected from a narrow or broad distribution, both centred at 500Hz with standard deviations of 0.5 and 1.5 octaves respectively. Occasionally embedded were two types of probe tones, a standard probe with a frequency equal to the mean of the distribution (i.e. 500 Hz), or an odd probe with a frequency two octaves above the mean (i.e. 2000 Hz). While listening to the sound stream, participants were asked to report changes in the luminance of a fixation cross. Half of the visual changes were accompanied by a deviant

probe tone. In the stimuli with the narrow context, this probe tone was an outlier to the distribution of other tones, while with the broad context, the probe was less likely to be an outlier. It was found that the deviant probe evoked faster responses to the luminance changes in the visual task and larger MMN responses when it was embedded in the narrow context, suggesting that even simple statistics like the variance of the frequency distribution can be encoded.

Nevertheless, as highlighted by Heilbron and Chait (2017), one of the most intriguing (MMN-related) facts is that the MMN is also evoked by the absence of an expected stimulus (for example, Yabe et al., 1997). This was observed as "one of the most remarkable properties of the auditory system" (Wacongne et al., 2012, p. 3671) and interpreted as strong evidence for predictive coding as "the auditory system [acquires] an internal model of regularities in auditory inputs, including abstract ones, that are used to generate weighted predictions about the incoming stimuli" (Wacongne et al., 2012, p. 3671). This surprising effect can also be succinctly explained as an indicator of prediction error in the process, whereby the presence of an incoming signal was strongly predicted but its absence flagged an error.

Automaticity

Another feature of the MMN response is that it is irrespective of attention; this has been widely demonstrated (e.g., Näätänen, 1992; Näätänen et al., 1993, 1978). The MMN response can be measured when the listener is distracted from the stimulus by performing unrelated tasks, not performing any tasks at all, during non-attentive states such as sleep (Atienza et al., 1997; Sallinen et al., 1994), or even in a coma (Fischer et al., 1999; Morlet and Fischer, 2013). Thus, this response is considered largely pre-attentive, suggesting that the encoding of regularities in the ongoing signals is an automatic process without attentive action.

Due to the limited processing capacity of the brain, it is impossible to constantly devote full attention to every detail in the surrounding environment. As such, the process of automatically extracting regularities plays a crucial role in our ability to detect and rapidly respond to changes in the environment, a factor critical to survival. This enables the monitoring

of the surrounding environment without the need for constant attention, thereby serving as an "early warning device" and rapidly directing attention to new objects and events in the environment.

1.2 Capturing the element of surprise

1.2.1 Uncertainty in the dynamic world

As discussed previously, according to the predictive coding, when novel information is received, beliefs are updated in proportion to the discrepancy between expectation and reality, called the prediction error. Unexpected signals may indicate an abrupt change in the environment and carry critical, survival-relevant, information; thus, the aim is to capture the element of surprise and act upon it.

In reality, most perceptually-relevant environmental statistics are highly dynamic, changing from one pattern to another. Optimised performance requires rapid and accurate updates to internal models of the external environment, particularly in unstable situations.

However, this is a complex task. Samples extracted from unstable sources must be weighted by their relevance; after a change in the environment's underlying statistics, newer samples are more relevant than older samples as they better reflect the new environment and accordingly would allow better predictions of the future. In a Bayesian statistical framework, optimal inferences and predictions from unreliable observations in a rapidly changing environment require the representation and manipulation of different forms of uncertainty. This uncertainty can be employed advantageously while learning (Behrens et al., 2007; Yu and Dayan, 2005), allowing the weighting of new and old samples when updating internal models and beliefs – a form of novelty detection which includes the quantification and appreciation of the probability that the underlying statistics have changed at each time point (Yu and Dayan, 2005).

The identification of the source of the prediction error is critical for learners in order to effectively weigh new and old samples when updating internal models. Is the error merely due to random fluctuations in the environment, or an important indication of change in the surroundings?

Stochastic changes, or noise, can be considered as *expected uncertainty* in the sensory input, and leveraged to further develop the internal model about the surrounding environment. This form of uncertainty is an inherent property of the sensory input and can be fully predicted even when all outcomes are unknown. For example (Yu and Dayan, 2005), deciding whether to carry an umbrella requires integrating and analysing many samples of information, which may come from weather forecasts, glance out of a window, and yesterday's weather. Occasionally, the weather forecast may be inaccurate, and this possibility is an *expected* uncertainty. However, if the forecast suddenly becomes increasing inaccurate, then this is an *unexpected* uncertainty, and seeking alternative sources would be prudent.

This *unexpected* uncertainty indicates an *abrupt* event which violates the expectation based on the preceding input. It can also be considered as a form of *surprise* (Dayan and Yu, 2006), indicating that a critical change-point has just occurred and the existing internal presentation about the ongoing signal is no longer valid. Considering the potential significance of such abrupt changes, unexpected uncertainty should be associated with (possibly automatic) responses to invalidate and disconnect from the out-dated models, and then promote learning for new models, in order to keep the internal model accurate and up-to-date. This can be employed to control the weights of new samples as further evidence of a change accumulates. Unexpected uncertainty is a label to indicate a sample which is surprising in the face of previously learnt contextual associations and regularities, even after accounting for expected uncertainties.

Expected vs unexpected uncertainty

While both expected and unexpected uncertainty play complementary roles in representing the external world, they signal completely different information and differ in their

fundamental statistical nature. Both are hypothesised to decrease the weight of top-down information on representational inference, but expected uncertainty arises from the known unreliability of predictive relationships within a familiar environment, indicating that the external environment is as unstable as the internal model predicts. On the other hand, unexpected uncertainty is an abrupt event induced by contextual changes in the environment that produce sensory observations strongly violating top-down expectations.

Unexpected uncertainty also differs in its influence on learning rate (Behrens et al., 2007; Nassar et al., 2010; Yu and Dayan, 2005): the degree at which that new information integrates with the old by changing the weights for each update epoch. To optimise inferences, not only does the brain need to track statistics in ongoing sensory signals, but also adapt its learning rate accordingly.

1.2.2 The Locus Coeruleus-Norepinephrine System

Achieving optimal inferences and learning requires the brain to track the statistics which underpin the sensory environment and to rapidly adapt internal models accordingly, especially when facing rapidly changing and unexpected signals.

Having established the importance of identifying unexpected uncertainty, how is this registered by the brain? A strong candidate has been proposed to be the neuromodulator norepinephrine (NE; also known as noradrenaline) (Baxter and Chiba, 1999; Bouret and Sara, 2005; Dayan and Yu, 2003; Gu, 2002; Posner and Petersen, 1990; Robbins and Everitt, 1995; Sara and Bouret, 2012; Sarter and Bruno, 1997; Yu and Dayan, 2005). Once something in the environment has changed unexpectedly, NE is proposed to "facilitate task-driven phasic behaviours and promote selective behaviour responses" (Rajkowski et al., 2004) by delivering a functional resetting signal (Bouret and Sara, 2005) to the rest of the brain. According to Bouret and Sara (2005), "a functional reset" is triggered by sensory evidence showing that the brain's model of the environment is no longer valid, and induces reorganisation of the relevant neural networks, ensuring that expectation-based top-down influences on processing are

interrupted immediately, and allowing behavioural adaptation in ever-changing environments. Details about this hypothesis and relevant evidence will be reviewed subsequently.

Anatomy: Widespread noradrenergic projections

In mammals, NE is generated by the locus coeruleus (LC) which is a cluster of neurons located in the dorsorostral pons of the brainstem and the sole source of NE of the entire brain (Moore and Bloom, 1979). The extensive projections starting from the LC connect all brain regions (with the exception of the basal ganglia) (Aston-Jones and Cohen, 2005; Aston-Jones and Cohen, 2005; Berridge and Waterhouse, 2003; Jones and Moore, 1977; Joshi et al., 2016; Murphy et al., 2014; Song et al., 2017). Thus, the idea that NE acts as an interrupt signal at transition periods is feasible; with its widespread intrusion, the LC noradrenergic (LC-NE) system has a capability to spread the signal across the entire brain rapidly and trigger potentially relevant cognitive functions, for example, decision-making and motor execution, in response to unexpected changes happened in the environment.

Physiology: The two modes of LC neural activity

Usher et al. (1999) noticed that the noradrenergic neurons of the LC have two different activity modes. In one of the modes, the firing rate of these neurons in the LC fluctuates around a certain level, while in the other mode the firing rate of the LC neurons suddenly increases dramatically and drop back to the baseline in a brief period (Aston-Jones et al., 1994). The former mode is called *tonic* LC activity, which means the baseline firing rate of the LC neurons, and it is associated with tonic NE level in the brain. The latter mode is called *phasic* LC activity which is associated with bursts of NE release in the brain.

These two activity modes are evident in a series of early studies performed by Aston-Jones et al.(Aston-Jones et al., 1994, 1997; Usher et al., 1999). In these studies, the activity of LC neurons was studied through direct neuronal recording with a simple oddball-detection task, in which monkeys were tasked with releasing a lever when seeing an infrequently appearing target while ignoring frequently-appearing distractors. Following the appearance of

a target and the associated decision outcome, LC neurons exhibited a strong phasic activation with slow tonic firing, while at most only a weak phasic response to distractors.

This target-evoked phasic LC response has five key characteristics: Firstly, the phasic response is very brief, lasting around 100ms. Secondly, the phasic response normally occurs very rapidly under one second (e.g. Aston-Jones et al., 2000, 1997, 1994; Bouret and Sara, 2004; Rajkowski et al., 2004; Sara and Segal, 1991; Usher et al., 1999; Vankov et al., 1995) and leads the relevant behavioural response by 200ms (Aston-Jones et al., 1994). Thirdly, the latency of the phasic response is significantly correlated with that of behavioural responses across trials, suggesting a tight coupling between phasic LC activity and behaviour. Fourthly, the magnitude of the phasic response is linked to the task performance of the trial (Aston-Jones et al. 1994; Usher et al. 1999); better task performance (higher accuracy and quick response) is observed with stronger LC phasic response. Fifthly, this response evoked by the target is not specific to physical properties of the stimuli (Aston-Jones et al., 1997; Bouret and Sara, 2004).

Meanwhile, although the precise mechanism remains unclear, NE is understood to mediate the neural gain of its target cortical structures by heightening neural sensitivity, in a process called gain modulation. For example, the application of NE in the primary auditory cortex leads to the simultaneous enhancement of sensory stimulus-evoked responses (“signal”) and reduction of background spontaneous neuronal activity (“noise”) (Foote et al., 1983; Segal and Bloom, 1976; Waterhouse and Woodward, 1980). Thus, this boosting effect of NE on the signal-to-noise ratio in cortical structures (Hasselmo et al., 1997; Sara, 1985; Servan-Schreiber et al., 1990; Woodward et al., 1979) enables NE to act as a gate for incoming sensory information by determining whether the information will be further processed. This gating effect of NE has been reported in many areas connected with the LC (Foote et al., 1983), including the frontal areas, hippocampus, and the thalamus. Taken this gating effect of NE and the task-related elicitation of the phasic LC activity together, it suggests that phasic LC

activity might have the ability to selectively boost the processing of relevant sensory information.

The level of tonic LC activity is known to be closely associated with the level of arousal; the higher the tonic LC activity, the higher the level of arousal. However, the relationship between arousal level and behavioural performance is complex: Extremely low levels of arousal may result in the inability to engage with any demanding cognitive task, even resulting in the inability to react to factors necessary for survival, while extremely high levels of arousal may cause anxiety. Essentially, arousal levels at the extremes of high or low both cause poor task performance. In fact, previous experimental data shows that the level of tonic LC activity is indeed closely related to task performance; when tonic LC activity is too low, subjects tend to make more mistakes (Aston-Jones et al., 1992, 1996; Usher et al., 1999), however when tonic LC activity is too high, subjects have a greater tendency to be distracted away from the task at hand (Aston-Jones et al., 1996, 1997). In other words, only when the tonic LC activity is within an intermediate range, can optimal performance be achieved. Interestingly, phasic LC activity has also been found to be completely diminished when tonic LC activity is too low or too high; in other words, high phasic LC activity is only observable when tonic LC activity is at an intermediate level (Aston-Jones et al. 1994). This again highlights a close relationship between the phasic LC activity and the preferential processing of task-relevant stimuli, which in turn maintains task focus and engagement.

In summary, the activities of the NE expressing neurons in the LC operate in two different modes: phasic and tonic; they are tightly coupled to the participant's behaviour and task performance – a transition from a high-tonic no-phasic mode to a low-tonic high-phasic mode is associated with an increase in alertness and an improvement in task performance.

Theories about the role of the LC-NE network

Currently, there are two leading theories regarding the role of the LC-NE system in attention and behaviour: The adaptive gain (Aston-Jones and Cohen, 2005) and unexpected uncertainty theories (Bouret and Sara, 2005; Dayan and Yu, 2006; Yu and Dayan, 2005).

The adaptive gain theory

According to the adaptive gain theory, LC phasic and tonic modes and task performance share a relationship reflecting a classic Yerkes-Dodson curve (Yerkes and Dodson, 1908): an extremely low tonic LC activity is associated with sleep and other low-arousal related phenomena, while an extremely high tonic LC activity is associated with a hypo-active status at which participants are prone to get distracted, and thus disengage with the default task they are performing, and in both of these two situations, phasic LC activity is absent; by contrast, at an intermediate level of tonic LC activity, the LC fires phasically, and participants can concentrate on and engage with the task that they are performing. In other words, phasic LC activity peaks at an intermediate level of tonic LC activity, and optimal performance is associated with high phasic LC activity. Aston-Jones and Cohen (2005) proposed that this provides a possible neural mechanism for the regulation of a balance between exploiting well-known options (e.g. choose a familiar dish that you know and like) and exploring new ones (e.g. try a new dish); this is called "exploitation-exploration balance", which is a dilemma commonly involved in decision-making, especially in unfamiliar and changing environments (Jepma and Nieuwenhuis, 2011). Phasic LC activity is hypothesised to drive exploitation of the current environment or task, but if the tonic LC activity exceeds the intermediate level optimal for phasic LC activity, the subject tends to disengage from the incumbent task, and explore alternative tasks as the environment evolves.

The unexpected uncertainty theory

The unexpected uncertainty theory hypothesises that: (1) Tonic LC activity reflects uncertainty about the probability of incoming input; the greater the uncertainty in the ongoing input, the higher the tonic activity. (2) Phasic LC activity is hypothesised to convey a form of surprise to the rest of the brain to inform an abrupt, unexpected and substantial change just happened in the ongoing input and called for initiation of updates for the internal models (Bouret and Sara, 2005; Dayan and Yu, 2006; Yu and Dayan, 2005).

Importantly, this relationship between NE and unexpected uncertainty agrees with the adaptive gain theory, providing a more specific explanation about how NE acts to optimise

behaviour. The unexpected uncertainty theory is also in agreement with other views of phasic NE response. For example, phasic NE responses have been implicated to facilitate the role of NE in exploitation by acting as an interrupt signal (Ego-Stengel et al., 2002) or initiating a broad functional reset (Bouret and Sara, 2005; see also, Dayan and Yu, 2006; Hermans et al., 2011; Marshall et al., 2016; Sara and Bouret, 2012). Such signal is meant to ensure that expectation-based top-down influences on processing are interrupted immediately when the sensory evidence has indicated that the brain's model of the environment is no longer valid.

Evidence for the role of NE in unexpected uncertainty

The early electrophysiological studies on the two modes of LC neural activity have shown a strong but broad indication of NE's participation in behavioural optimisation. Since optimising inferential and learning processes require continuous tracking of the environment's underlying statistics to rapidly adapt internal models to reflect the external world, especially when facing unexpected signals, how is NE involved in this process? Thus, this section explores the evidence for the role of NE as signalling unexpected uncertainty.

Substantial influences on top-down and bottom-up signals

A precondition for NE as an interrupt signal is that it should be able to influence the regulation of sensory information processing. Accumulating evidence has shown that NE satisfies this condition, for example, NE plays an inhibitory role on synaptic formation in the visual cortex (Parnavelas and Blue, 1982) which allows suppression of the top-down expectation-based signals. More recently, Kobayashi et al. (2000) reported that increases in NE suppress top-down signals while sparing bottom-up signals in the visual cortex, which provides direct evidence that NE plays an important role in mediating the balance between top-down expectation-based and bottom-up sensory-driven signals.

Meanwhile, NE is also known to have an effect of promoting learning about new contexts (see review Gu, 2002). In primary sensory cortices, the exhaustion of NE has been observed with a suppression effect on experience-dependent plasticity (Bear and Singer, 1986; Levin et al., 1988), while the increase of NE induces experience-dependent, long-lasting

modifications of neuronal responses (Greuel et al., 1988). These effects allow NE to revise the internal representations based on new experiences and promote learning of new relationships which contradict existing knowledge, which is consistent with the theoretical notion of unexpected uncertainty.

Moreover, with its widespread neural network, NE has the capability of signalling changes across the whole brain at once; this makes NE well placed to rapidly coordinate the broad functional resetting process (Bouret & Sara, 2004).

NE signals unexpected uncertainty

However, NE is not the only neuromodulator that can produce these cortical effects. Acetylcholine (ACh) is also known to be capable of influencing top-down signals (Gil et al., 1997; Hasselmo et al., 1996; Hsieh et al., 2000; Kimura et al., 1999) and have an effect on the cortical reorganisation (Ego-Stengel et al., 2001; Kilgard and Merzenich, 1998; Metherate and Weinberger, 1990).

Nevertheless, ACh is not responsible for unexpected uncertainty because it has been found selectively engaged in tasks which involve expected, but not unexpected, uncertainty. A common paradigm used to investigate expected uncertainty is the probabilistic cueing paradigm. One example is the Posner task, in which a cue foretells the location of its associated target with a certain probability. Comparing trials with valid and invalid cues, participants process the targets with increased speed and accuracy with correct cues; the difference in performance increases as the validity of the cues improves, the so-called validity effect (Bowman et al., 1993; Downing, 1988). Here, the probability of invalid cues is a measure of the task's random nature as learned by the participants, and therefore constitutes an expected uncertainty. Studies on rodents, primates (Phillips et al., 2000; Witte et al., 1997), and humans (Chiba et al., 1999; Parasuraman et al., 1992; Voytko et al., 1994; Whitehouse et al., 1982; Witte et al., 1997) have observed that the validity effect is anticorrelated with the neural activity of the ACh expressing neurons of the nucleus basalis, suggesting that ACh suppresses the use of invalid cues.

However, it is hard to capture and measure the response to unexpected uncertainty in the Posner task. Thus, studying unexpected uncertainty requires a different paradigm, in the form of another classic attentional paradigm called the attention-shifting paradigm. Participants must observe stimuli with certain predictive relationships, and occasionally the experimenter deliberately changes the relationships without informing the participants. This task allows the study of how participants shift attention between cues to discover the new relationships by themselves. For example, Devauges and Sara (1990) used a maze navigation task to investigate the effect of boosting NE on learning. In that study, rats must solve a sequential decision problem with two sets of cues – spatial and visual – that indicate which route they must take in order to proceed from one end of the maze to the other. After a few days of learning, the relevant valid cue would be suddenly switched from spatial to visual cues without warning. After the unexpected cue switch, rats who were treated with the NE-boosting drug idazoxan (Curet et al., 1987) learned to use the alternative set of cues faster than the controls (Devauges and Sara, 1990). More recently, McGaughy et al. (2008) found that noradrenergic, but not cholinergic, lesions in the rat prefrontal cortex impaired the ability to shift attention from one task to another. These findings suggest that while a lack of NE would result in the inability to switch tasks, elevated tonic NE accelerated exploring and learning of the new relationships.

In a seminal computational study, Yu and Dayan (2005) proposed that NE is selectively involved in unexpected uncertainty while ACh is involved in expected uncertainty. To directly compare the roles of NE and ACh under a unified framework, they introduced a new task, combining the Posner and the attention-shift tasks – the “Extended Posner Task” – in which participants observe a sequence of trials, each containing a cue frame followed by a target frame after a variable delay, and must respond as soon as they detect the target. The cue frame contains a set of coloured arrows randomly pointing to left or right, with one of the arrows predicting the target location with a significantly higher probability than the others. As in the Posner task, in each trial, participants need to implicitly evaluate the cue validity of each cue

and predict the likelihood of the target location given with the cue; this cue validity is inversely correlated with the expected uncertainty. Just like the attention-shift task, a sudden change in the cue identity (colour) and validity (likelihood to predict the target location correctly) could happen without warning, and this gives rises to unexpected uncertainty. Thus, in this task, expected and unexpected uncertainty can be manipulated at different stages of the task. The model parameters representing NE and ACh were selectively active at different stages of the task, with NE involved in unexpected uncertainty and ACh in expected uncertainty.

Another paradigm to model unexpected uncertainty employs a gambling task (e.g. the Iowa Gambling Task from Bechara et al., 1994), which requires participants to actively learn a series of winning probabilities and predict outcomes that return positive results. This paradigm has been used in a few studies (Jepma and Nieuwenhuis, 2011; Lavín et al., 2014; Payzan-LeNestour et al., 2013; Preuschoff et al., 2011; Satterthwaite et al., 2007), where unexpected uncertainty was manipulated via sudden changes in the outcome probability distributions. The BOLD response was measured with the participant was viewing the outcomes; unexpected uncertainty has been found to be correlated with BOLD activity in the human left LC (Payzan-LeNestour et al., 2013).

Moreover, tonic BOLD activity in the brain areas that have projections from the LC, including the posterior cingulate cortex, bilateral postcentral gyrus, left middle temporal gyrus, left hippocampus and left posterior insula, was found to have a significant correlation with unexpected uncertainty arising from the decision-making process.

A recent human pharmacological study (Marshall et al., 2016) used prazosin – an inverse agonist for α-1 receptors – to investigate the influence of NE on learning rate during a visual pattern identification task. Prazosin has clinical applications in the treatments of high blood pressure and anxiety, and is orally active which is undoubtedly an advantage for experimental operation. In the Marshall et al. (2016) study, participants were presented with a series of four visual stimuli with a stimulus onset asynchrony of 1.4s, and participants reported the identification of each stimulus by pressing a corresponding button. A probabilistic rule

governed the stimulus order, which was reconfigured every 70 seconds without notification to the participant. Hence participants who managed to learn the underlying rules would be expected to respond more quickly. The authors used a computational model, the Hierarchical Gaussian Filter (HGF) (Mathys et al., 2014), which estimates an individual's learning rate based on their response times as the trials progress. Administering a noradrenergic antagonist – prazosin – was indeed found to selectively impair the learning of uncertainty arising from changes in the environmental context.

These experimental results provided some evidence for the unexpected uncertainty hypothesis: the LC-NE system plays a critical role in processing the unexpected changes in the ongoing sensory input, and the level of tonic LC activity might reflect uncertainty about the probability of incoming input. However, apart from the tonic LC activity, there is also a much faster component of NE signalling – phasic LC activity – which has been proposed to signal abrupt, unexpected changes in a much rapid scale (Bouret and Sara, 2005; Dayan and Yu, 2006).

This idea is in line with previous observations of phasic NE response in the form of novelty detection. Strong phasic LC activity has been consistently observed in direct recordings of LC neurons, immediately after an unexpected change in physical properties of sensory stimuli (Carli et al., 1983; Rajkowski et al., 1994; Sara et al., 1994). Interestingly, even when freely exploring in a new environment, detection of novel objects would also evoke strong phasic NE responses, suggesting that the effect of novelty detection on phasic NE response is robust and not affected no matter whether the participant remains still or is walking (Vankov et al., 1995).

Also, it has been indicated an association between phasic NE responses and the P3 component of the event-related potential (Nieuwenhuis et al., 2005, 2011). P3 is an electrophysiological signature for conscious detection of expectation violations, and has shown sensitivity to novelty (Donchin et al., 1978), surprise (Verleger et al., 1994), and oddballs

(Pineda et al., 1997), which again supports the hypothesis that phasic NE response signals unexpected uncertainty.

Recently, pupil diameter has been discovered to closely track LC-NE activity and therefore become a very attractive non-invasive, convenient and inexpensive means to investigate the human LC-NE system. Thus, the following section will focus on the relationship between the noradrenergic activity in the brain and pupillary responses and the evidence for its reliability. Afterwards, a review of evidence for phasic NE signalling unexpected uncertainty will be presented.

1.3 Pupil size as a proxy of noradrenergic activity

1.3.1 Relationship between pupil size and LC activity

The idea that pupil size and NE neuronal activity fluctuation in the LC are tightly correlated was first reported in a preliminary analysis of single cell recordings in a monkey target detection experiment (Rajkowski et al., 1993), where the pupil diameter baseline was found to strongly mirror the tonic LC firing rate, implying that changes in pupil size are closely linked to LC activity, with higher *baseline* pupil diameter (pupil is constantly large) reflecting high tonic activity and lower baseline pupil diameter reflecting phasic activity (as phasic activity is absent when tonic activity is very high) (Figure 1.2).

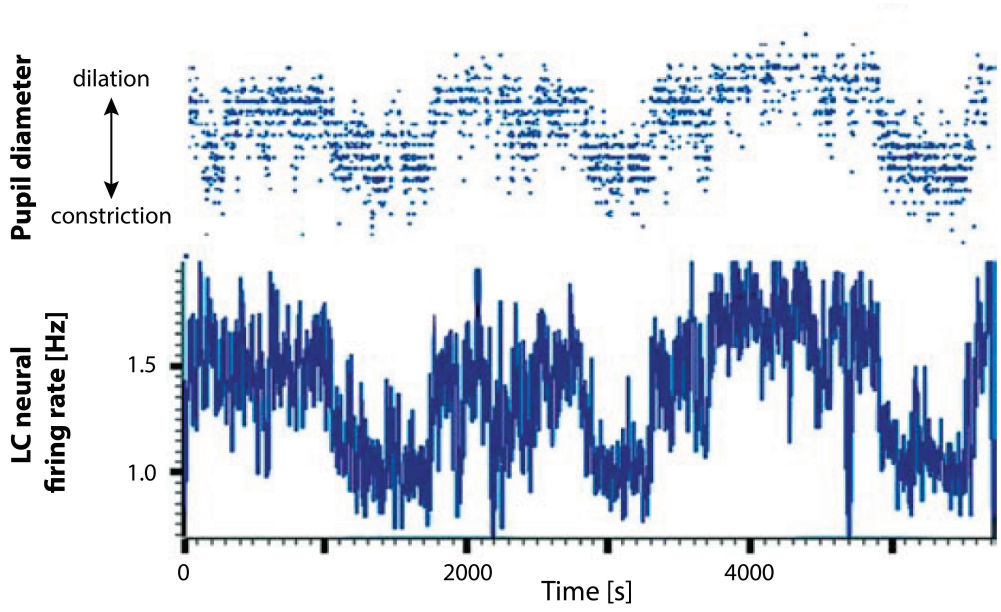


Figure 1.2 Relationship between LC neuronal activity and pupil diameter. Tight temporal coupling between the firing rate of an NE-expressing neuron in the LC and pupil diameter of a monkey during a target detection task. Adapted from Rajkowski et al. 1993.

In the last decade this finding has gained much traction, leading to the attractive possibility of employing this physiological measure as a proxy for neuromodulation and activity measurements in this area of the brain (Aston-Jones and Cohen, 2005; Joshi et al., 2016; McDougal and Gamlin, 2015; Nassar et al., 2012; Reimer et al., 2016). Recent human

neuroimaging investigations into fluctuations in pupil diameter and LC activity found a significant positive correlation between the continuous pupil diameter and blood-oxygen-level-dependent (BOLD) activity in the rostral LC, both at rest and during task performance (Murphy et al., 2014). This is also supported by early human pharmacological studies, which found that the α_2-noradrenoceptor agonist clonidine, which causes a decrease in tonic NE level by activating the inhibitory α_2-noradrenoceptor on noradrenergic neurons in the LC, is associated with a decrease in baseline pupil diameter (Bitsios et al., 1998, 1996; Clifford et al., 1982; Fanciullacci et al., 1988; Phillips et al., 2000). On the other hand, the α_2-noradrenoceptor antagonist yohimbine leads to enhanced tonic LC activity and has been observed with increased baseline pupil diameter (Morley et al., 1991; Phillips et al., 2000).

Moreover, the inverse relationship between phasic activity and tonic activity (Usher et al., 1999; reviewed in the previous section) has also been observed in human pupillometric data, as an inverse correlation between transient pupil dilation and baseline pupil diameter (Gilzenrat et al., 2010): with a high pupil diameter baseline, task-relevant signals elicit small or no transient pupil dilation responses. However, from this, one question remains: Is this null-effect of transient pupil dilation responses merely a reflection of the saturation effect of the pupil diameter? It would appear that this question has not been addressed in past literature, thus this thesis will directly address and describe this saturation hypothesis in detail in a later chapter (Chapter 5).

Furthermore, a human electrophysiological study on the P3 component of the event-related potential which might be a cortical electrophysiological correlate of the *phasic* LC response (Nieuwenhuis et al., 2005, 2011) found that the amplitude of P3 was greater when the pupil diameter baseline was at an intermediate level (Murphy et al., 2011). These observations are consistent with human pharmacological studies, which found that the administration of Modafinil is characterised by high phasic LC activity – shown by functional magnetic resonance imaging (fMRI) (Minzenberg et al., 2008) – and is associated with a lower pupil diameter baseline (Hou et al., 2005). Modafinil is a wakefulness-promoting drug which

increases vigilance level (Edgar and Seidel, 1997; Panckeri et al., 1996; Shelton et al., 1995), and importantly, it affects NE by inhibiting the NE transporter (Madras et al., 2006).

The strong correlation between pupil size changes and LC activity has recently been further confirmed by Joshi et al. (2016) who investigated pupil dynamics by directly recording neuronal activity in the LC and many parts of the LC-NE network in macaque monkeys, including the inferior colliculus (IC), superior colliculus (SC), anterior cingulate cortex (ACC) and posterior cingulate cortex (PCC). First, they investigated the relationship between pupil diameter and neural spiking rate while the monkeys' pupils were fixated passively and not doing any tasks, finding that spontaneous fluctuations in pupil diameter consistently correlate with spiking rates in all five of these brain regions, but particularly strongly in the LC and IC: for example, epochs with larger pupil diameters were associated with a higher baseline spiking rate in LC. Additionally, they found an even stronger relationship when comparing pupil diameter with individual neuronal spikes; in particular, the LC neurons tended to fire 305ms before pupil dilations. Furthermore, when examining the relationship between neuronal activity and pupil responses in the context of external events (for example, unexpected brief auditory stimuli), they discovered that unexpected auditory stimuli evoked stable transient pupil dilations, and importantly, amongst these five brain regions only the LC showed a reliable link with pupil responses on a trial-by-trial basis. This is consistent with the results of Reimer et al. (2016) whose work on mice demonstrated that rapid pupil dilations were closely associated by phasic LC activities both when the wakeful mice were still and walked. Hence, this series of findings highlights the reliability of pupil size as a proxy for LC activity.

1.3.2 How does the LC-NE system mediate pupil size?

Accumulating evidence has linked neural activity in the LC-NE system with the changes in the pupil size, but how does the subcortical region LC influence the eye?

In the eye, pupil size is controlled by two sets of smooth muscles in the iris, the dilator and sphincter muscles, which are activated by distinct sources. The dilator muscles – which

dilate the pupil – receive noradrenergic input from the sympathetic nervous system, while sphincter muscles constrict the pupil via cholinergic input from the parasympathetic system. In this manner, pupil diameter is governed by the balance between the effects of these two sets of muscles; in other words, changes in pupil diameter is a result of interaction between the sympathetic and parasympathetic pathways (Einhäuser, 2017; Loewenfeld and Lowenstein, 1993; Szabadi, 2012; Widmann et al., 2018). More details about pupillometry will be given in Chapter 2.

Thus far, the precise mechanism behind the regulation of the sympathetic and parasympathetic pathways and high-level cognition remains unclear. Particularly, despite the intriguing correlation between neuronal activity in the LC and the pupil diameter, the exact mechanism effecting this relationship is still unknown and is considered a challenge amongst researchers using pupil size as a measurement of the LC-NE activity (Gilzenrat et al., 2010; Joshi et al., 2016; Nieuwenhuis et al., 2011).

However, the LC has direct inhibitory projections to the Edinger-Westphal (EW) nucleus (also called the accessory oculomotor nucleus) which supplies parasympathetic nerve fibres to the sphincter muscles. Thus, the LC-mediated pupil dilation could be an indirect consequence of inhibiting the EW nucleus, which in turns inhibits pupil constriction (Beatty and Lucero-Wagoner, 2000; Loewenfeld and Lowenstein, 1993).

In addition to the inhibition of pupil constriction, a human pharmacological study found that the cognition-related pupil dilation is also affected by the activation of dilator muscles which receives inputs from the sympathetic system (Steinhauer et al., 2004). This is not unreasonable when considering that NE is the main mediator in the sympathetic system, with early studies (e.g. Elam et al., 1986) reporting correlations between activity in the LC and sympathetic nerves. However, there are no known candidate pathways which directly arbitrate this effect – one possibility is the paragigantocellularis nucleus in the ventral medulla(Hilton and Smith, 1984; Loewy et al., 1981; Samuels and Szabadi, 2008a, 2008b).

1.3.3 ACh tracks long-lasting pupil dilations during walking

It is worth noting that NE expressed in the LC is not the only neuromodulator system that mediates non-luminance changes in pupil size. Acetylcholine (ACh), as noted above as a proposed neuromodulator for expected uncertainty, has also been known to be associated with pupil diameter (Reimer et al., 2016; Zaborszky et al., 2015). More specifically, in contrast with NE, ACh was found to be more related with pupil dilations during locomotion. This difference has been demonstrated by Reimer et al. (2016) on mice during stillness and walking. When the mice remained still, the onset of the rapid pupil dilations closely followed the phasic NE activity, while the correlation between the pupil dynamics and the activity in ACh expressing neurons was much weaker. When the mice were walking, the large, long-lasting locomotion-related pupil dilations were accompanied by sustained ACh activity, while NE exhibited strong responses along with pupil dilation only when the mice were just starting to walk (Reimer et al., 2016). Overall, Reimer et al. (2016) noted that while sustained ACh activity followed motor responses more closely, the transient pupil dilations during periods of stillness – which is also the interest of this thesis – appeared to tightly track phasic NE activity.

Nevertheless, this highlights that despite the strong correlation between pupil diameter fluctuations and LC activity, NE is not the only agent mediating this interaction, and thus caution should be exercised when interpreting LC-mediated pupil responses.

1.3.4 Pupillometric evidence for the adaptive gain theory

Notwithstanding the lack of understanding of the link between the LC and pupil diameter dynamics, there is an increasing wealth of evidence – gained by directly comparing neuronal activity in the LC and concurrently recording pupil diameter – that supports correlations between the two, making pupillometry a very attractive means to examine the LC-NE system, and especially so for testing theories on the role of the LC-NE system. Interestingly, although the relationship between pupil and the LC activity was discovered more than 20 years ago (Rajkowski et al., 1993), it was only mentioned in a conference poster and

not widely disseminated until the authors Aston-Jones and Cohen included it in their influential review published in 2005, in which they also proposed their well-known adaptive gain theory. As noted above, according to the adaptive gain theory, the LC-NE system plays a key role in optimising task performance by balancing between *exploitative* and *exploratory* behaviours: Starting with relatively low tonic LC activity, as the tonic LC level increases, performance improves as participant alertness and task focus increases (more exploitative), however, once the tonic LC level exceeds a certain degree, the participant becomes distractible and tends to disengage from the default task (more exploratory), resulting in a decrease in tasks performance. In a direct investigation of exploitative and exploratory choices, Jepma and Nieuwenhuis (2011) used a four-armed bandit task in which human participants must repeatedly choose between four slot machines to maximise monetary gain. As the payoffs of the four machines gradually and independently vary from trial to trial, participants must balance between exploitative (e.g. “continue with this machine”) and exploratory choices (e.g. “try a different machine which might deliver higher winnings”). It was found that pre-choice pupil diameters (i.e. baseline pupil diameter) were larger before exploratory choices than exploitative choices, suggesting high tonic LC activity associated with an exploratory behaviour; this is a result predicted by the adaptive gain theory.

Moreover, in several human studies, baseline pupil diameter (again, assumed to reflect the level of LC tonic activity) has been consistently reported to be negatively correlated with the behavioural performance (Eldar et al., 2013, 2016; Gilzenrat et al., 2010; Jepma and Nieuwenhuis, 2011). Pre-stimulus baseline pupil diameter exhibits a U-shaped relationship with reaction time when performing a challenging auditory detection task (i.e. quickest reaction times at intermediate pre-stimulus pupil diameters) in humans (Murphy et al., 2011) and mice (McGinley et al., 2015), in agreement with the adaptive gain theory’s notion on tonic LC activity.

The adaptive gain theory has also been supported by multiple pharmacological (non-pupillometry) studies in animals and humans, showing that behavioural engagement can be modulated by drugs targeting the LC-NE system. For example, rats and monkeys exhibited

increased attentional shifting and reversal learning with drugs which increase tonic NE activity (Lapiz et al., 2007; Lapiz and Morilak, 2006; Seu et al., 2009; Steere and Arnsten, 1997). In humans, cognitive flexibility was found to be associated with drug-induced high tonic NE level, as administration of atomoxetine – a selective NE reuptake inhibitor (Zerbe et al., 1985) which induces NE increase in prefrontal cortex by occupation of NE transporter (Bymaster et al., 2002) – improved in the ability to disengage from the default task (Chamberlain et al., 2006) and has been used in the treatment of attention deficit hyperactive disorder. Likewise, enhanced social flexibility, indicated by an increase in social interaction and a reduction in self-focus, was found to be associated with Reboxetine-induced high tonic NE activity (Tse and Bond, 2002).

1.4 Pupillometric evidence for phasic NE as an interrupt signal

As reviewed above, accumulating evidence from human and animals has shown that pupil diameter is a potential proxy of LC-NE activity in the brain, with baseline pupil diameter reflecting tonic LC activity and transient pupil dilation reflecting phasic LC activity. As reviewed at the end of the last section, human pupillometric data have provided promising evidence for the adaptive gain theory (Aston-Jones and Cohen, 2005), mainly derived from the relationship between baseline pupil diameter and tonic LC activity. Likewise, pupillometry is also a very attractive means to test the other LC theory – the unexpected uncertainty theory (Bouret and Sara, 2005; Dayan and Yu, 2006; Yu and Dayan, 2005) which proposed that phasic NE signals unexpected uncertainty and delivers interrupt signals, based on the knowledge that transient pupil dilations can act as an indicator for phasic LC activity. Following from this, this section continues to review evidence for the role of NE in unexpected uncertainty with a specific focus on evidence from human pupillometric studies.

1.4.1 Phasic NE and novelty detection

Consistent with observations of phasic NE response to unexpected external changes, transient pupil dilations have been long known to be evoked by deviant sensory stimuli. An inverse relationship between the pupil size and stimulus probability has been known for some time (Friedman et al., 1973; Liao et al., 2016b; Nieuwenhuis et al., 2011; Qiyuan et al., 1985; Raisig et al., 2010). Pupil dilations in barn owls are observed to frequency and location deviants in an ongoing tone stream (Bala and Takahashi, 2000); in humans and monkeys, pupil dilation responses can be evoked by audio-visual stimuli, consisting of visual contrast differences and auditory intensity changes (Wang et al., 2014; Wang and Munoz, 2014). More recently, Liao et al. (2016b) and Wetzel et al. (2016) observed human pupil dilation evoked by oddball auditory stimuli embedded in a repetitive tone sequence. Moreover, under passive listening condition, Liao et al. (2016b) found that the amplitude of the pupil dilation response was associated with the contrast between the deviant and the standard stimuli: when there are two different deviant types – e.g. one deviant type is 2000Hz pure tone, and another type is white noise – embedded in the repeating standard (1000Hz pure tone) sequence, the deviant who is more different from the standard would evoke a larger pupil dilation response. This finding was consistent with Liao et al. (2016a), which demonstrated that pupil dilation varied with the perceived salience of brief natural sounds.

1.4.2 Phasic NE and changes in statistics

Data from both novelty and deviant detection studies support a model where NE reports unexpected environmental changes, thereby performing as an alerting system for contextual switches. However, in reality, sensory input and contextual switches are much more convoluted than repeating tone sequences with sparsely inserted deviants.

Recently, in addition to responding to deviant stimuli, pupil size has been found to track changes in stimulus predictability. In Nassar et al. (2012), human participants were asked to predict the next number in a random sequence of numbers chosen from a Gaussian distribution

with a mean that changed at random intervals (change-points), in other words, the sequences were “generated from a change-point process” (Krishnamurthy et al., 2017). Nassar et al. (2012) found, as tracking complex and noisy data, when the participants realised the occurrence of a change-point – i.e. an unexpected uncertainty, a transient pupil size increase could be observed in the participants’ eye. Moreover, the transient pupil size increase was found to positively correlate with the change-point probability or the subject’s confidence that the source of the prediction error was a fundamental change-point. Considering this transient pupil size increase reflecting the phasic LC activity in the brain, these findings suggest that phasic LC activity is involved in the active sequence tracking process and it might specifically relate with signalling the occurrence of unexpected uncertainty in the sequence which the participant is actively monitoring.

A similar finding was reported by Preuschoff et al. (2011), who instead of presenting a digit on a screen, presented the digit via auditory instruction. Participants were presented with two digits (numbered 1 through 10) in serial and before the first to-be-heard digit, they needed to bet which digit (first or second) would be bigger. The pupil after the first digit signals the risk (a form of expected uncertainty): If, after knowing the first digit is a “9”, the subject bets that the 1st digit is higher, the resulting risk of loss (or expectation of error) is low. Pupil response after the second digit signals the surprise (unexpected uncertainty): The more certain participants feel about the outcome, the greater the resulting surprise from a prediction error. Indeed, Preuschoff et al. observed a positive association between the amplitude of pupil dilation and the surprise (unexpected uncertainty). The usage of auditory stimuli here, instead of visual stimuli, greatly diminished the severe confound of pupillary light reflex from the pupil data.

Krishnamurthy et al. (2017) reported similar findings with a dynamic sound-localisation task, a modification of the predictive inference task used previously. In this study, instead of tracking digits, participants were asked to continuously track sequences of sounds which came from different locations; the structure of these sound sequences was generated from a change-

point process as in their previous study (Nassar et al., 2012). The locations of the sounds were sampled uniformly randomly along a horizontal plane, and occasionally, the mean of the distribution of the sampled locations suddenly changed, resulting in an unexpected change in the distribution of upcoming sound locations. Sporadically, the sequence would also stop, requiring the participants to predict and report the next sound's (probe sound) location. Then, the sound would be played, with the subject expected to report its perceptual position. The probe sound differs in the reliability and relevance of preceding sounds with its position along the sequence (e.g. within a stable period or at the change-point). The authors analysed the tonic pupil response, which is the baseline pupil diameter before the presentation of the probe sound, and the phasic pupil response, which is the transient pupil dilation following the probe sound. They found that both of these pupil responses were affected by perceptual bias, and specifically, the amplitude of the transient pupil dilation was selectively strongly negatively correlated with prior relevance – the probability that a newly arriving information is consistent with recent history, or in other words positively correlated with "unexpected uncertainty" – while the baseline pupil diameter was strongly correlated with the reliability of the preceding sounds ("expected uncertainty"). This again provides evidence that the evoked pupil dilation, reflecting phasic NE response, express the unexpected uncertainty in the sequence which the participants are actively tracking.

These human pupillometry findings all demonstrate a strong indication that LC-mediated pupil dilations are sensitive to abrupt changes in statistics in actively-tracked stimuli, even when the stimuli are complex stochastic signals, and simultaneously provide evidence for the involvement of phasic NE response in signalling unexpected uncertainty, at least when the brain is actively tracking the changes in the sequence.

1.4.3 Limitations of the previous studies

Overall, as reviewed above, the results from many studies – drawn from direct neural recording, neuroimaging and pupillometry on rodents, monkeys and humans – strongly

implicate the tonic and phasic activity modes of the LC-NE system in modulating the influence of newly-arriving sensory information on internal models describing the external dynamic environment. However, two major questions remain.

Firstly, is NE response only associated with perceptual judgement? Previous studies into the role of NE have required participants to report the changes actively. Considering the potential importance of unattended changes in the environment, the role of NE should not be limited to decision-making processes. Moreover, as the decision-making process strongly affects pupillometry, these paradigms result in the non-trivial confounding of perceptual evidence accumulation with decision-making components.

Secondly, despite the fact that the phasic NE response has a surprisingly short latency (100–200ms) (e.g. Rajkowski et al., 2004; Usher et al., 1999), the paradigms used in the previous studies normally require perceptual judgements for every element in the sequence, so the presentation rate is unavoidably slow, on the order of seconds. However, if the signalling process of unexpected uncertainty is to provide a reliable basis for perception, considering that many sensory signals change much more rapidly (especially in some complex sensory scenarios), this signalling process must have the capability to operate over rapid timescales.

1.5 Introduction of new stimulus to model uncertainty

With a view to addressing these shortcomings, this chapter introduces and describes a new set of stimuli to study unexpected uncertainty, along with detailed reviews of relevant work and inspiration. Here we choose to use auditory stimuli to study unexpected uncertainty by pupillometry. There are three advantages of using auditory stimuli:

Firstly, as reviewed at the beginning of this chapter, it is widely accepted that the human auditory system possesses a remarkable ability to track embedded statistics in the acoustic environment. Accumulating evidence has shown that human listeners can readily extract

complex structures from acoustic signals. This capability is understood to be a result of the highly-structured and pattern-driven nature of the acoustic world; the auditory system leverages the recurring features of these patterns to catalogue assign sources to incoming sensory information, allowing categorisation of future input (Bregman, 1990). These patterns – such as those in rain, footsteps, or language – shape the unique signatures for their sources, as indicated by the successes in reconstructing sound textures of natural sounds by synthetic models (McDermott et al., 2009, 2011, 2013) and is evident in the computational attempts to model natural sounds using extracted structures over different time-scales (Turner and Sahani, 2008). The extraction of these patterns is essential to understanding the acoustic environment, enabling the brain to identify and segregate sounds of disparate sources from the background scene (Bendixen et al., 2007, 2010, 2012; Denham and Winkler, 2006; Winkler, 2007; Winkler et al., 2009).

Secondly, the auditory system has shown automatic and rapid detection of changes in the environment. Acting as an early-warning system, the auditory system connects us 24/7 with the external world by continuously scanning for opportunities and dangers even when we are not actively searching them. Learning established patterns extracted from auditory input enables the prediction of successive signals, and importantly, flag mismatches of expectation, which has been extensively indicated in many studies on MMN.

Thirdly, using auditory stimuli can avoid effects caused by the pupillary light reflex – the most severe confound in pupillometry. These all inspired us to use the auditory system as a test-bed to investigate the NE signalling processes.

1.5.1 Rapid tone-pip sequences conveying complex frequency patterns

As illustrated in Figure 1.3, the stimuli are constructed from rapid sequences of concatenated 50ms tone-pips (gated with 5ms raised cosine ramps) with frequencies drawn from a pool of 20 log-spaced values between 222–2000Hz (at 12% steps, 1/6th of an octave).

Random patterns (*RAND*) are generated by randomly sampling frequencies from the pool with replacement, while regularly repeating patterns (*REG*) are constructed by randomly selecting (with replacement) a number of frequencies from the pool (10 frequencies in this example) and then iterating that sequence to create a regularly repeating pattern (with new patterns generated per trial).

Compared with RAND, REG is highly precise (i.e. the prediction based on the REG sequence is very reliable) and has much less variability of the sensory evidence. Thus the REG sequence should have a lower expected uncertainty than the RAND sequence.

By concatenating these sequences, transitions between regular and random patterns can be constructed. A transition from regular to random patterns (REG-RAND) can be taken as a violation of regularity which should lead to *an unexpected uncertainty*, while the reverse – random to regular (RAND-REG) – can be taken as an emergence of regularity which should lead to *a gradual decrease in expected uncertainty*, or in the framework of predictive coding, should induce an increase in precision.

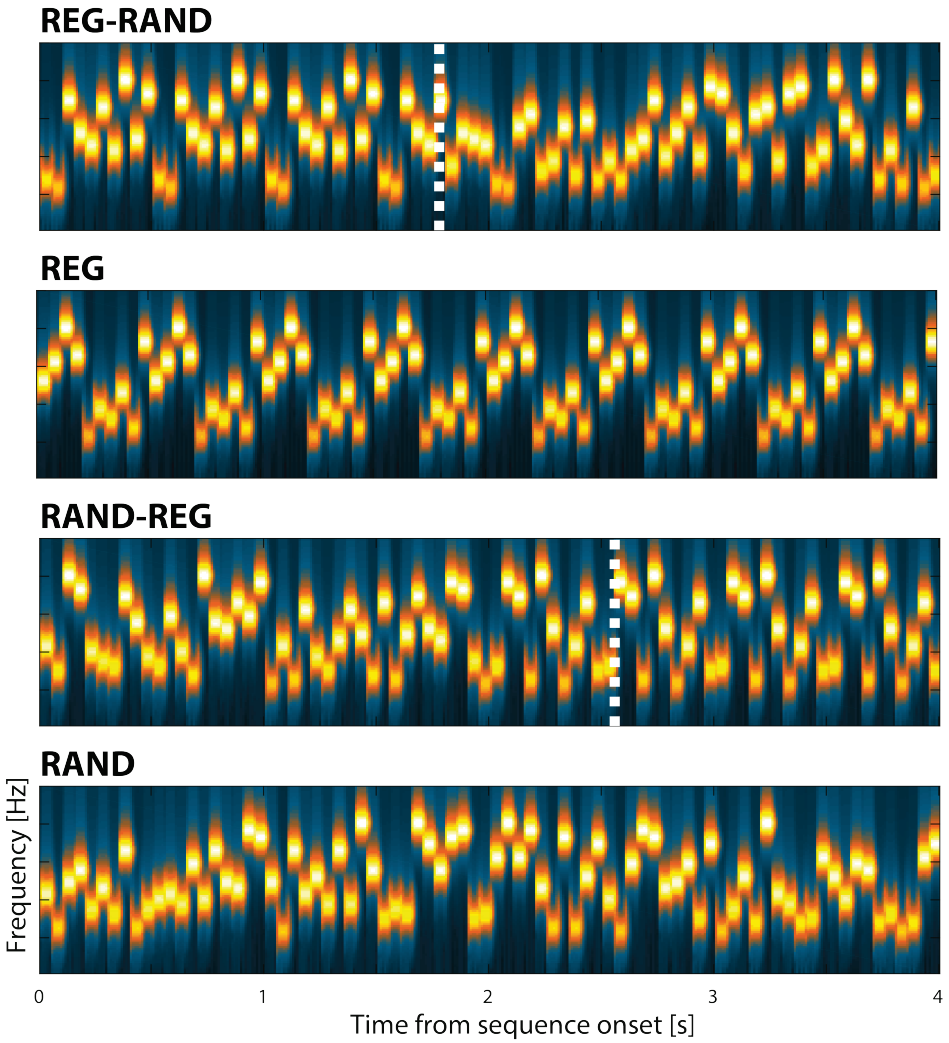


Figure 1.3 Representative auditory spectrograms of the stimuli used in Barascud et al. (2016). Transition sequence REG-RAND (a transition from a regularly repeating pattern to a random pattern) and its no-change control REG sequence. Transition sequence RAND-REG (from a regularly repeating pattern to a random pattern) and its no-change control RAND sequence. The transitions are indicated by a vertical dashed line. All stimuli are generated anew for each subject. The auditory spectrograms shown in this work were all generated with a filter bank of 1/ERB (Equivalent Rectangular Bandwidth) wide channels.

For REG-RAND, the signals are generated such that at the transition the first tone in the RAND sequence always violates the REG pattern. Therefore, the transition should be detected after the first tone in the RAND sequence. For RAND-REG, the first cycle of the regularity is not detectable because listeners need to wait for the repetition to detect that regularity is present. Therefore, the transition time is set to the onset of the second cycle of the regular cycle.

The tone duration of 50ms (20Hz) was deliberately chosen to ensure that the tempo of the sequences remains too rapid for the applicability of any form of reasoned decision making (Warren and Ackroff, 1976; Warren et al., 1991; Warren, 2008; Warren and Obusek, 1972); in this manner, initial perception of an emergence of regularity can be described to "pop out" from the ongoing stimuli and thus maintain independence from individual subjective effort.

One of the most important advantages of this stimulus design is that it affords considerable flexibility in the degree of complexity of the patterns involved. The complexity level of the pattern can be controlled by varying the size of the frequency subset ("alphabet size") from which the tones are randomly sampled.

Most importantly, these sound sequences can provide a simplified abstract representation of our complicated ever-changing acoustic environment with a limited number of discrete frequency values. In this simplified acoustic world, there are only 20 auditory filters in the auditory system, and 20 possible frequencies in 50ms units. The frequencies of the 20 tones are sufficiently spaced to allow adjacent frequencies to be distinguishable. Although the number of elements is not very large, it is enough to generate different frequency patterns (a regular or random pattern, or just a single repeating tone) with a certain degree of complexity. By simply concatenating different frequency patterns, changes from one pattern to another can be easily manipulated.

1.5.2 A review of relevant works using this stimulus

This set of stimuli was first developed by Chait et al. to investigate the process of regularity encoding (Barascud et al., 2016; Southwell et al., 2017).

Behaviour: Rapid detection of auditory pattern changes

In a behavioural experiment (Barascud et al., 2016), participants were instructed to detect transitions in REG-RAND and RAND-REG stimuli actively. The presence of a transition was unpredictable, as transition trials were jittered every trial and were randomly shuffled amongst an equal number of non-transition trials.

In addition to the four frequency patterns (REG, RAND, REG-RAND and RAND-REG), two additional patterns featured in the behavioural experiment: *CONST* sequences consisted of a single repeating (constant) tone, chosen by randomly selecting the frequency from the pool on each trial (Figure 1.4); *STEP* sequences consisted of a step change between two repeating tones (randomly drawn each trial) (Figure 1.4). STEP was included as it is the simplest form of a pattern change that can be represented in this type of rapid frequency-varying sequences. To obtain a lower bound measure of computation time to detect the transition (detection time), each subject's reaction time to STEP stimuli was employed as a basic reaction time to an obvious auditory change and subtracted from the reaction times to REG-RAND and RAND-REG changes. The transition times in STEP sequences were also randomly jittered in the same manner as REG-RAND and RAND-REG, and trials of STEPs were presented randomly amongst other sequences, including an equal number of trials of its control CONST.

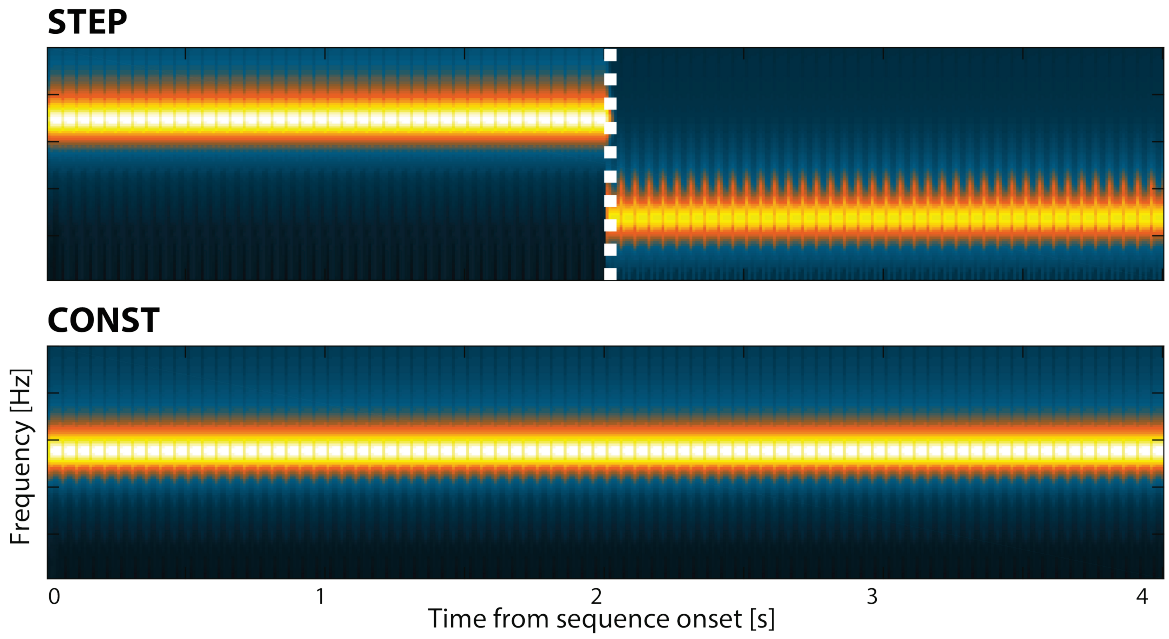


Figure 1.4 Representative auditory spectrograms of the STEP and CONST stimuli.

To benchmark how much information was needed to detect these transitions, an unsupervised machine-learning model of auditory expectancy (Information Dynamics Of Music, IDyOM[1], Pearce, 2005) was used to quantify the predictability of each tone-pip within the sequences. Given a sequence of tones, the model produces estimations of the probability distribution of all successive tones and outputs information content as a measure to quantify expectedness.

For RAND-REG, this ideal observer model required only an additional half-cycle of the regular pattern to detect the emergence of regularity (Figure 1.5B), requiring 4 to 5 tones to discover a regular pattern of ten tones. Intriguingly, active listeners also required a similar number, 277ms (5.5 tones), suggesting that human listeners to need only an additional half-cycle of a regular pattern to discover the emergence of regularity. This indicates that human performance is comparable with an ideal observer gifted with perfect memory and attention, demonstrating the remarkable ability of the human brain to detect pattern changes in rapid complex sound sequences.

In theory, the violation of regularity in REG-RAND should be detectable at the first tone in RAND. Indeed, as shown in Figure 1.5C, the ideal observer model showed an effectively instantaneous detection to the transition in REG-RAND and detected at the first post-transition tone. The behavioural results (Figure 1.5A) showed that on average listeners needed 155ms (3.1 tones), more sluggish than the ideal observer. The disparity in performance lagging by 100ms (2 tones) was statistically significant.

Currently, it is unclear why human listeners show such a disparity in performance, slower by more than three tones than the model when detecting the violation of the regularity,

[1] More details about the model is available on https://code.soundsoftware.ac.uk/projects/idyom-project

while showing ideal-observer performance when detecting the emergence of regularity. One possibility for this difference is that compared to the detection of regularity emergence, the process of violation detection might involve extra process(es) in addition to sensory evidence accumulation, such as some manner of checking process to ensure that the learned regularity has indeed been violated and avoid over-reaction to unimportant fluctuations in the sensory environment.

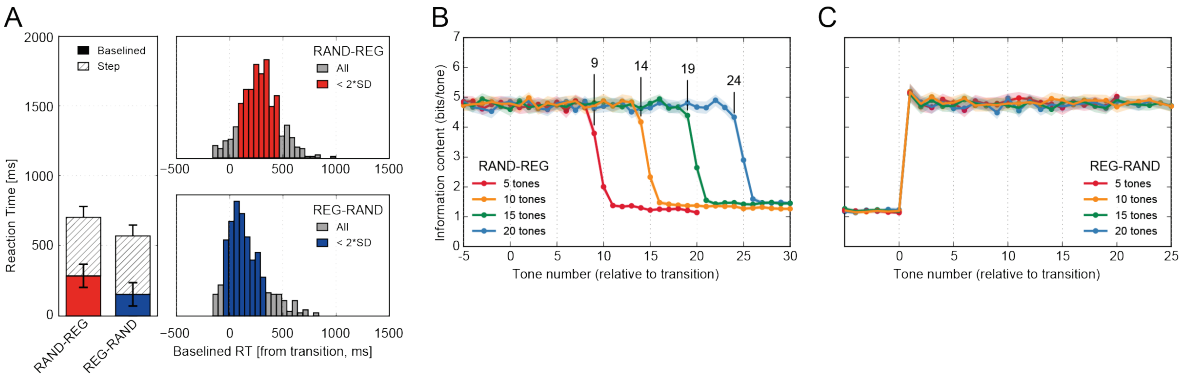


Figure 1.5 Behavioural and modelling results for REG-RAND and RAND-REG. Both transitions are equally well detectable, and human listeners detected them as quickly as an ideal observer model (IDyOM). [A] Average reaction time and reaction time distribution. [B] Model result showing the average information content for each tone for RAND-REG with varying repeating regularity lengths (REG5, REG10, REG15, REG20 with lengths of 5, 10, 15 and 20 respectively) are also presented. Regardless of the regularity length, the model could detect the emergence of regularity after only one cycle and four tones. Shaded error bars are two standard deviations from the mean. [C] Model result is showing the average information content for each tone for various REG-RAND transitions. The model detected all REG-RAND transitions immediately after the first RAND tone. Again, shaded error bars are two standard deviations from the mean. Reproduced from Barascud et al. (2016).

MEG and fMRI brain responses to rapid sequences

MEG brain responses of naive passive listeners showed similar patterns in the transition detection latency. In the MEG experiment, a group of new participants naïve to the auditory stimuli were presented with the same stimuli (REG-RAND, RAND-REG and their controls) while distracted from the sound by performing an incidental visual task: participants were tasked with reporting repeated images amongst groups of three landscape photographs. The measured brain responses can, therefore, be taken as reflecting largely automatic processes.

Generally, the brain activity evoked by both transitions (Figure 1.6) is characterised by large-scale DC shifts, on which responses to individual tones (20 Hz) are superimposed. Evoked responses consist of an onset peak (M100) at around 100ms post-onset, and subsequent rise to a sustained response and offset response is observed shortly after the end of the sequence. The mean response to the transition from random to regular pattern commences about 250ms after the transition and is manifested as a gradual increase in amplitude (over 250ms; 5 tones) and a subsequent plateau. This reveals that the passive listener's brain also only needs a half-cycle to detect the emergence of regularity, which echoes the active behavioural and ideal-observer modelling results.

The response to the violation of regularity (REG-RAND) was characterised by an MMN-like response (a small power increase around 150ms post-transition; Figure 1.6A top), followed by a sharp decrease in DC power which occurs immediately after the MMN response. The response to REG-RAND started to diverge from its control over 200-250ms (4-5 tones) post-transition, which, consistent with the active behavioural result, was significantly slower than the ideal observer's performance. This lag in response to REG-RAND was also visible at a single trial level (Figure 1.6B), and very consistent across trials with a peak value around 250ms. The response to the emergence of regularity (RAND-REG) was found to be associated with a gradual and substantial increase in large-scale, sustained cortical response (Figure 1.6A). This pattern of cortical responses to these two transitions was very interesting for three main reasons.

Firstly, both types of transitions evoked cortical responses which significantly differentiated from their corresponding no-change controls after the transition. This demonstrated that the brain is very sensitive to these changes in the patterns under passive listening condition. This might also reflect that listeners could automatically extract patterns and detect both transitions cortically, even when they were engaged in a change-irrelevant and relatively distracting task.

Secondly, the detection of the emergence of regularity was manifested as an *increase* in the sustained response, thus it could not be attributed to a low-level effect like neural adaptation, because in the studies of evoked potentials, adaptation effects were commonly observed as an attenuated response (Megela and Teyler, 1979; review see Pérez-González and Malmierca, 2014). Barascud et al (2016) suggested that while the sharp decrease in amplitude of the sustained response reflected the brain's detection of violation of regularity and involved error-signal indicating the sudden change in the internal model, the increased DC response for regular patterns was hypothesized to reflect the activation of a highly active top-down network that turns on when the brain discovers the sensory signal is predictable and persists until the brain disconnects this model following unexpected uncertainty.

Although the exact cause of this increase in the sustained cortical response for regular patterns as observed in MEG and EEG responses remains unclear, Barascud et al. (2016) suggested that it might reflect an increase in the predictability of the sensory input, indicating that tones in regular patterns are more predictable than those in random patterns. Southwell et al. (2017) provided three possibilities: The first possibility is that this regularity-associated cortical response enhancement might be due to an increase in synaptic inhibition rather than excitation, as these techniques cannot dissociate the two. Natan et al. (2015) supported this hypothesis, finding that inhibitory neurons in the primary auditory cortex play a critical role in encoding repeated sounds. The second possibility is that this sustained response reflects a distinct process or a combination of multiple processes, which may include learning or matching with memories as the source reconstruction result. The third possibility is that this amplitude increase is related to gain (increased neural sensitivity) in the relevant prediction error units activated by the regular pattern, but this precision-weighting process operates automatically and does not involve high-level attentional capture.

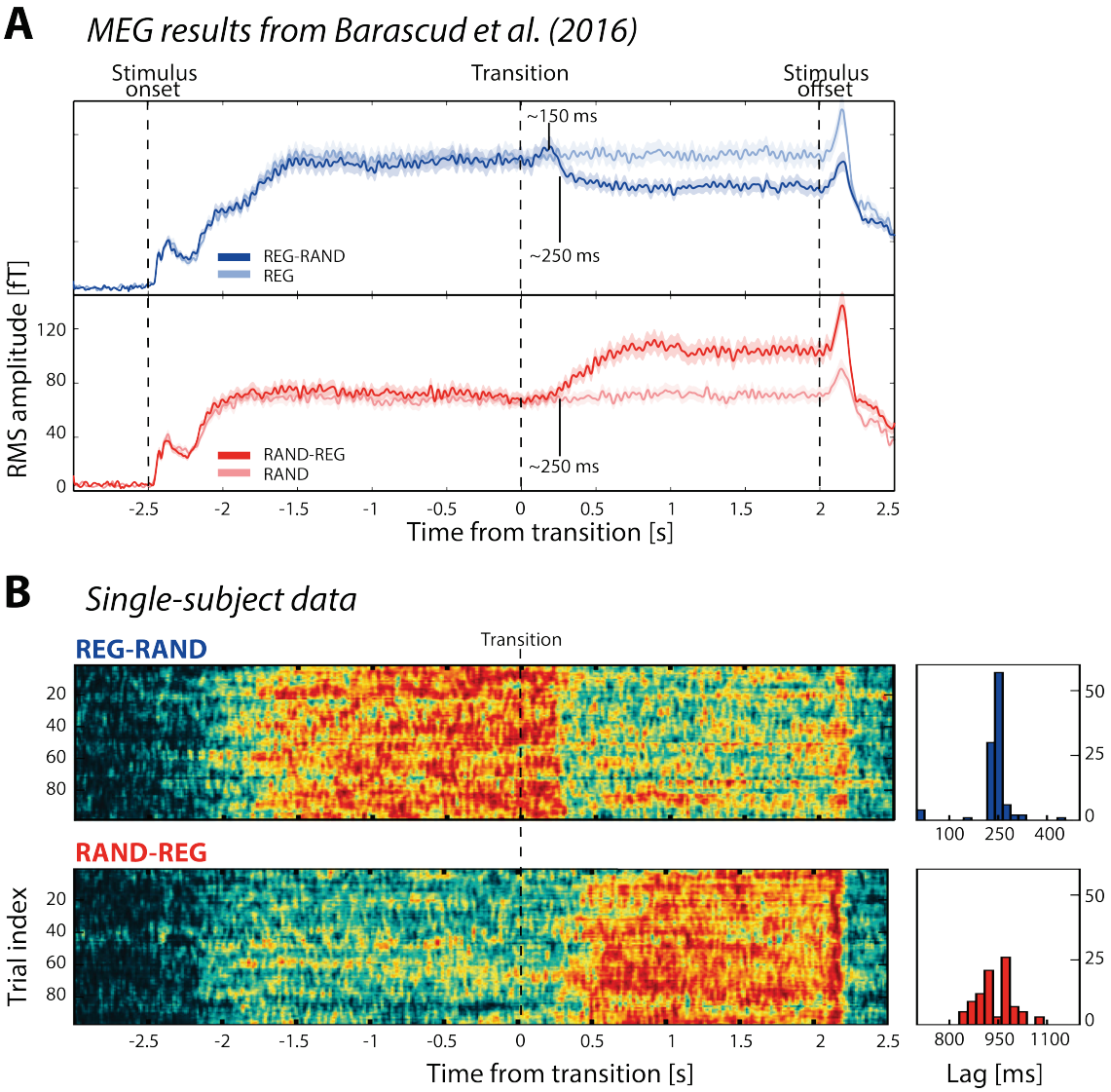


Figure 1.6 MEG responses to REG-RAND and RAND-REG. [A] The plots show mean responses (root-mean-square across auditory channels; 13 participants) of brain responses to REG-RAND (top panel) and RAND-REG (bottom panel) conditions, along with their respective no-change controls. The figures show the entire stimulus-epoch, from stimulus onset (−2.5s) to offset (2.5s). Shaded areas around the curves represent twice the standard error of the mean, computed with bootstrap resampling. [B] Single-trial data from a representative participant for REG-RAND (top) and RAND-REG (bottom). In each panel, on the left, the raster plots show the single trial data for each condition. The warmer the colour, the greater the MEG response. On the right, the histograms show the distribution of the temporal jitter in transition responses. The temporal jitter within each trial was estimated by cross-correlating the single trial root-mean-square time course with a descending (for REG-RAND) and ascending (for RAND-REG) Heaviside step function. The lags that gave the maximum correlation value for each trial are plotted in the histograms. Reproduced from Barascud et al. (2016).

Thirdly, the amplitude of the sustained response appears to be associated with the expected uncertainty carried by the sound sequence, or in the framework of predictive coding, the precision. Barascud et al. (2016) investigated cortical responses to sequences with varying complexity; for regular sequences the length of the cyclical pattern was varied, and for random sequences the alphabet size (number of different frequencies that the next tone could be randomly drawn from) was varied. Figure 1.7 shows the MEG responses to REG5, REG10, REG15 (regular repeating cycles with 5, 10 or 15 different tones respectively) (Figure 1.7A) and RAND5, RAND10, RAND15 (random tone sequences composed of 5, 10 or 15 different tones respectively) (Figure 1-7B), along with the response to RAND20 which has the highest expected uncertainty in this set of stimuli. The pattern of cortical responses demonstrated that the brain is sensitive to pattern structures, whether regular or random, as highlighted by the differentiated responses to REG5 and RAND5 (Figure 1.7C). Furthermore, the brain is sensitive to pattern complexity as manipulated by the alphabet size, as there are clear contrasts between the responses to REG5 and REG10 (Figure 1.7A and Figure 1.7B). This pattern was later replicated in EEG by Southwell et al. (2017) and also observed in another MEG study using artificial auditory scenes, constructed from layers of regular and/or random tone-pip streams (Sohoglu and Chait, 2016). Importantly, the relationship of the two sequence parameters – pattern structure and alphabet size – with the amplitude of the sustained response can be explained by expected uncertainty. For example, when comparing RAND5 (a random sequence composed of five different tones) and RAND10 (a random sequence composed of 10 different tones), RAND5 has a lower expected uncertainty, and accordingly, the response to RAND5 indeed has a greater amplitude (Figure 1.7B). Comparing REG5 and RAND5, REG5 has a lower expected uncertainty, and its resulting response also has a greater amplitude (Figure 1.7C). Thus, there is a patent possibility that the amplitude of the sustained response reflects the degree of expected uncertainty in the ongoing sensory signal, with smaller expected uncertainties eliciting the greatest sustained cortical response amplitudes.

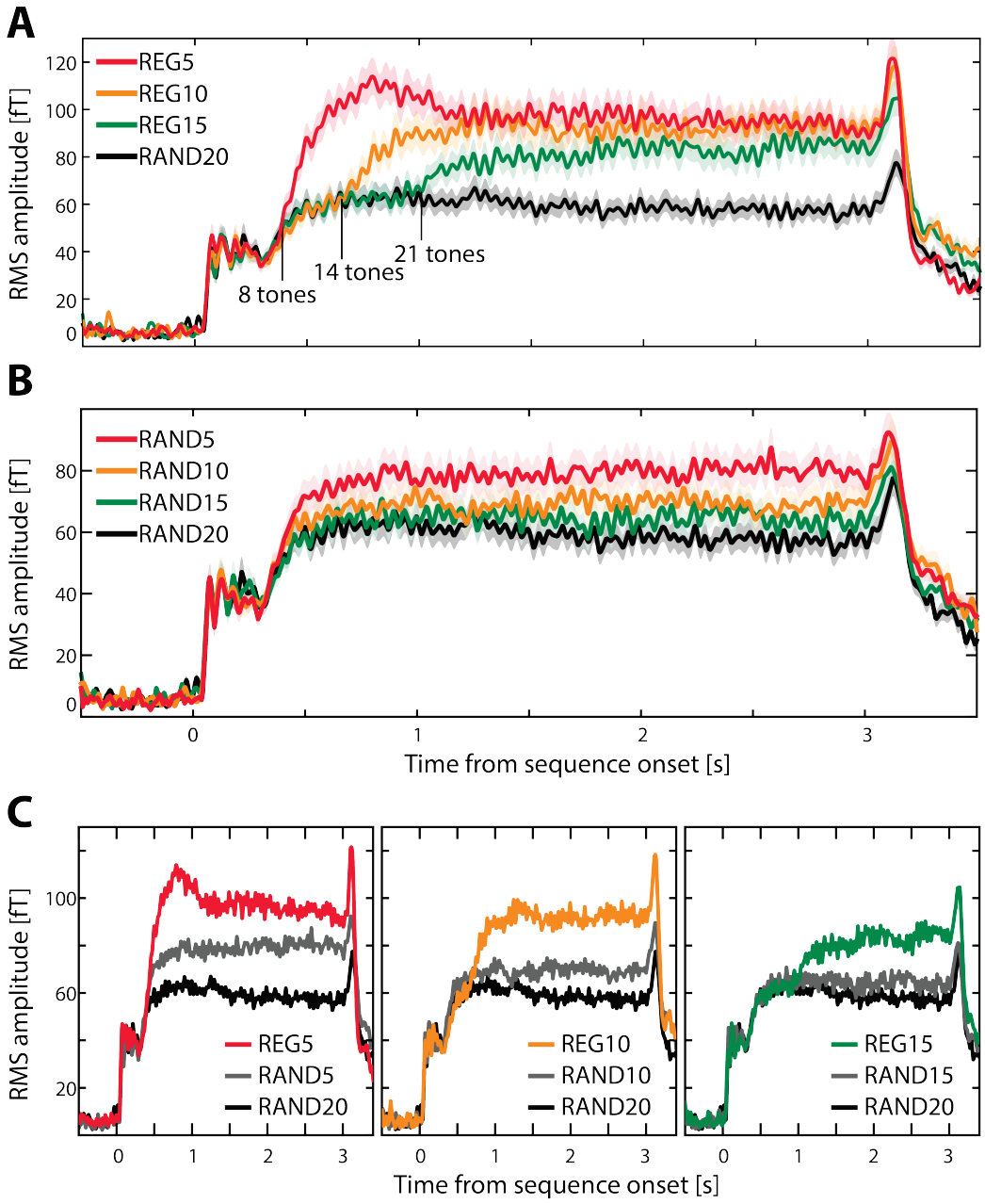


Figure 1.7 MEG responses to REG or RAND sequences with different alphabet sizes. [A] Mean responses (root-mean-square across auditory channels) to the regular sequences with different alphabet sizes: REG5, REG10, and REG15, compared to RAND20. Shaded areas around the curves represent twice the standard error of the mean, computed with bootstrap resampling. [B] Mean responses to the random sequences with different alphabet sizes: RAND5, RAND10, RAND15, and RAND20. [C] MEG responses to REG5, REG10, and REG15 (identical to those plotted in [A]) are plotted with their corresponding RAND sequences (RAND5, RAND10, RAND15) along with RAND20. The responses to the REG sequences are plotted in the colours identical to that in [A], and the corresponding RAND sequences are plotted in grey, with the RAND20 sequence is plotted in black. Reproduced from Barascud et al. (2016).

The MEG source localisation result (see Barascud et al., 2016, for details) showed that the regularity extraction process involves an increased activity in a network consisting of the auditory cortex (AC, bilaterally), inferior frontal gyrus (IFG, right side only) in the frontal cortex and hippocampus (bilaterally). The AC and right IFG have been consistently reported to be part of the network for the MMN (Garrido et al., 2009; Molholm et al., 2005; Opitz et al., 2002). The observed activity in the IFG was interpreted as an integral part of the predictive network associated with implicit learning and detecting changes in the ongoing sound sequences (Buchsbaum et al., 2005; de Vries et al., 2009; Gazzaley and Nobre, 2012; Makuuchi et al., 2009; Petersson et al., 2004; Ranganath et al., 2004; Zatorre et al., 1994). The hippocampus is considered to be involved in the integration of complex temporal patterns in audition (Geiser et al., 2014) and statistical learning (Covington et al., 2018) in other modalities, like vision (Turk-Browne et al., 2009, 2010).

The fMRI BOLD result further confirmed the involvement of AC and IFG in the process tracking statistics in the REG and RAND sequences. Considering the temporal limitation of the fMRI, this activation pattern was predominately associated with the sustained part in the MEG responses to REG and RAND, rather than the short evidence accumulation period indicated as a gradual increase in the MEG response. The BOLD responses to the REG and RAND revealed a very similar activation pattern, along Heschl's gyrus (HG) and planum temporale (PT) bilaterally. The contrast REG minus RAND also showed IFG activation but only significant in the left hemisphere.

These results suggest that the process of tracking rapidly evolving statistical structure in the sound sequences might be performed by a network comprised of the auditory cortex and frontal sources like IFG. This AC-IFG network is in line with the MMN literature in which the AC-IFG network has been shown to best explain the MMN generation (Chennu et al., 2016; Garrido et al., 2008, 2009, Phillips et al., 2015, 2016). The activation of IFG is also commonly observed along with the violation of complex artificial grammar under both passive implicit and

active explicit learning conditions (de Vries et al., 2009; Makuuchi et al., 2009; Petersson et al., 2004).

1.5.3 Further exploration of the statistical tracking process

Using these sound sequences, previous works (Barascud et al., 2016; Southwell et al., 2017) have primarily investigated how the cortical portions of the neural network tracks sequence statistics in auditory stimuli. Here, this study aims to further explore this statistical tracking process and extend investigations to the subcortical regions; more specifically, whether the LC is involved in the processing of auditory pattern transitions of this type.

Based on the functional imaging results reviewed above, this study proposes that the emergence and violation of regularity are processed in distinctly differently manners by the subcortical regions. Figure 1.8 illustrates a hypothesis describing a model for the processing of emergences of regularity under passive listening conditions. The onset of the random (RAND) sequence initiates the statistical tracking network of the cortex, which includes the auditory cortex (AC) and the inferior frontal gyrus (IFG). The AC-IFG network continuously tracks statistics in the rapid sound sequence and forms the internal model for the RAND pattern with growing expected uncertainty. This process can be observed as a gradual increase in the cortical response followed by an acoustic onset response in Barascud et al. (2016). Continuing with statistical tracking, the AC-IFG network maintains the internal model for the RAND pattern, and this pattern encoding process can be observed as a sustained cortical response with a relatively low amplitude, as low amplitudes are hypothesised to reflect the high expected uncertainty – or low precision – in the RAND pattern (Barascud et al. 2016). The statistical tracking process continues, and as the sequence transitions into the REG pattern, the AC-IFG network accumulates sensory evidence for the new pattern. Meanwhile, the internal model is gradually being updated, and the expected uncertainty gradually decreases as the highly precise regularity emerges; MEG results have revealed this process as a gradual increase in the sustained response. Once sufficient statistics have been accumulated, the internal model

for the REG pattern is continuously maintained by the AC-IFG loop which can be observed as a sustained MEG response with a relatively high amplitude reflecting the small expected uncertainty of the REG model. The discovery of a new patterns can thus be described as a non-stop process of continuous updates of internal models, with the expected uncertainty changing accordingly.

Figure 1.9 illustrates our working hypothesis for the processing of violations of regularity during passive listening. In a similar manner to the onset of the random sequence, the onset of the regular (REG) sequence should also initiate the AC-IFG statistical tracking network in the cortex. This network continuously tracks the statistics conveyed in the sequence and forms the internal model for the REG pattern with a relatively low expected uncertainty. The low expected uncertainty is associated with the relatively high sustained cortical response in MEG results (Barascud et al. 2016). With the advent of the random (RAND) pattern, the first tone in this new random pattern violates the precise regular pattern; this sensory signal falls outside of the existent model for the REG pattern and can be automatically detected by the AC-IFG network, which generates an MMN component observed in the cortical response (Barascud et al. 2016). The AC then activates the subcortical LC, which in turn activates a phasic NE response to deliver an interrupt signal to the rest of the brain, indicating that an abrupt violation of the existent model has just occurred and that an immediate disconnect from the existent internal model is required. The sharp decrease in the MEG response following the MMN component might be a reflection of this process. If this set of hypotheses is true, then based on previous works which show that the phasic LC response can be reliably observed in transition pupil dilation responses, it can be reasonably expected that this disconnect process should potentially be observed as a transient pupil dilation shortly after the REG-RAND transition even during passive listening.

This thesis will also include the STEP transition, which features the violation of repetition by introducing a deviant frequency, thus leading to novelty detection. As reviewed in the previous section, it has been well-established that deviant sensory stimuli evoke phasic

LC-NE responses and corresponding robust transient pupil dilation responses (Liao et al. 2016b, Wetzel et al. 2016). So far, according to current knowledge, no pulmometry studies have investigated transitions in rapid and complex auditory frequency pattern sequences. Thus, pupillary responses to the STEP transition will be employed as a benchmark for the sensitivity of the LC-NE system to changes in this type of stimuli.

The experiments which will be described in the following chapters of this thesis will provide a compelling test of the unexpected uncertainty theory – Dayan and Yu's model of the NE signalling of unexpected uncertainty in sensory signals. As illustrated in the hypotheses of the present study, transient pupil dilations are expected shortly after the STEP and REG-RAND transitions associated with unexpected uncertainty, but no pupil dilation after the RAND-REG transition, despite the fact that these transitions are all clearly perceptually detectable.

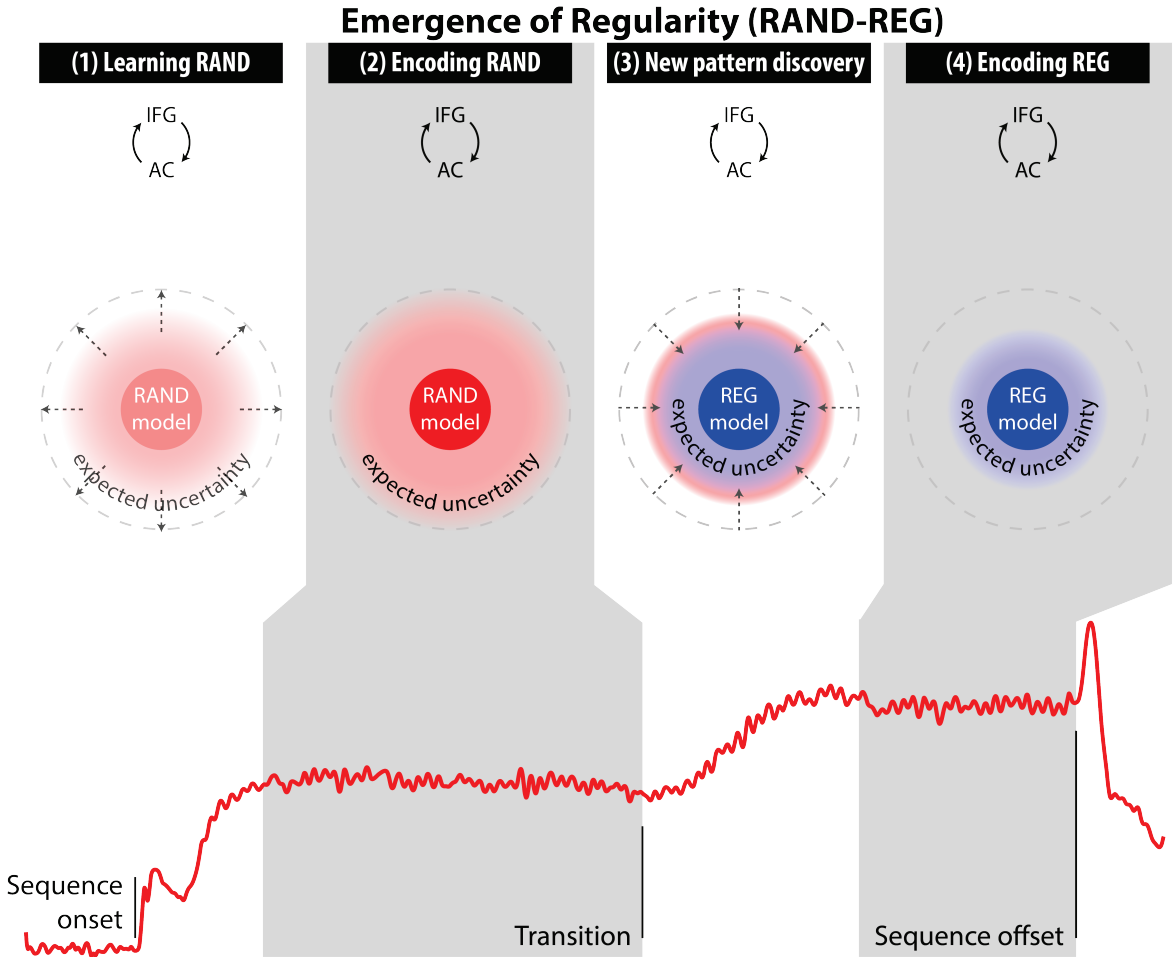


Figure 1.8 Hypothetical schematics for the processing of emergences of regularity (RAND-REG). The MEG response for the sequence changing from a random to a regular pattern is plotted at the bottom (adapted from Barascud et al. 2016). The entire process can be divided into four stages (indicated as four columns from left to right): (1) The cortical portion of the sequence statistical tracking network includes the auditory cortex (AC) and the inferior frontal gyrus (IFG). Starting from sequence onset, this network continuously tracks and gradually learns the statistics of the initial random (RAND) sequence, forming the internal model for the RAND pattern with increasing expected uncertainty (shown as a red circle). The expected uncertainty is illustrated as the shaded area surrounding the circle. This process can be observed as a gradual increase in the cortical response followed by an acoustic onset response. (2) The network continues tracking the statistics to maintain the accuracy of the internal model (illustrated as a solid red circle with the growing shaded red area). (3) After the transition, the AC-IFG network continues tracking the sequence and accumulates sensory evidence for the new regular (REG) pattern. On discovery of the new pattern, the internal model is gradually updated, and expected uncertainty gradually decreases as the highly precise regularity emerges. This is observed as a gradual increase in the sustained response to the MEG result. (4) Once sufficient statistical information has been accumulated, the REG pattern is continuously encoded by the AC-IFG loop in a process which can be observed as a sustained MEG response with a higher amplitude; the relatively low expected uncertainty of the internal model of the REG pattern is reflected in this higher amplitude. The discovery of new patterns is an unceasing process of delivering updates to the internal model,

during which the expected uncertainty changes accordingly.

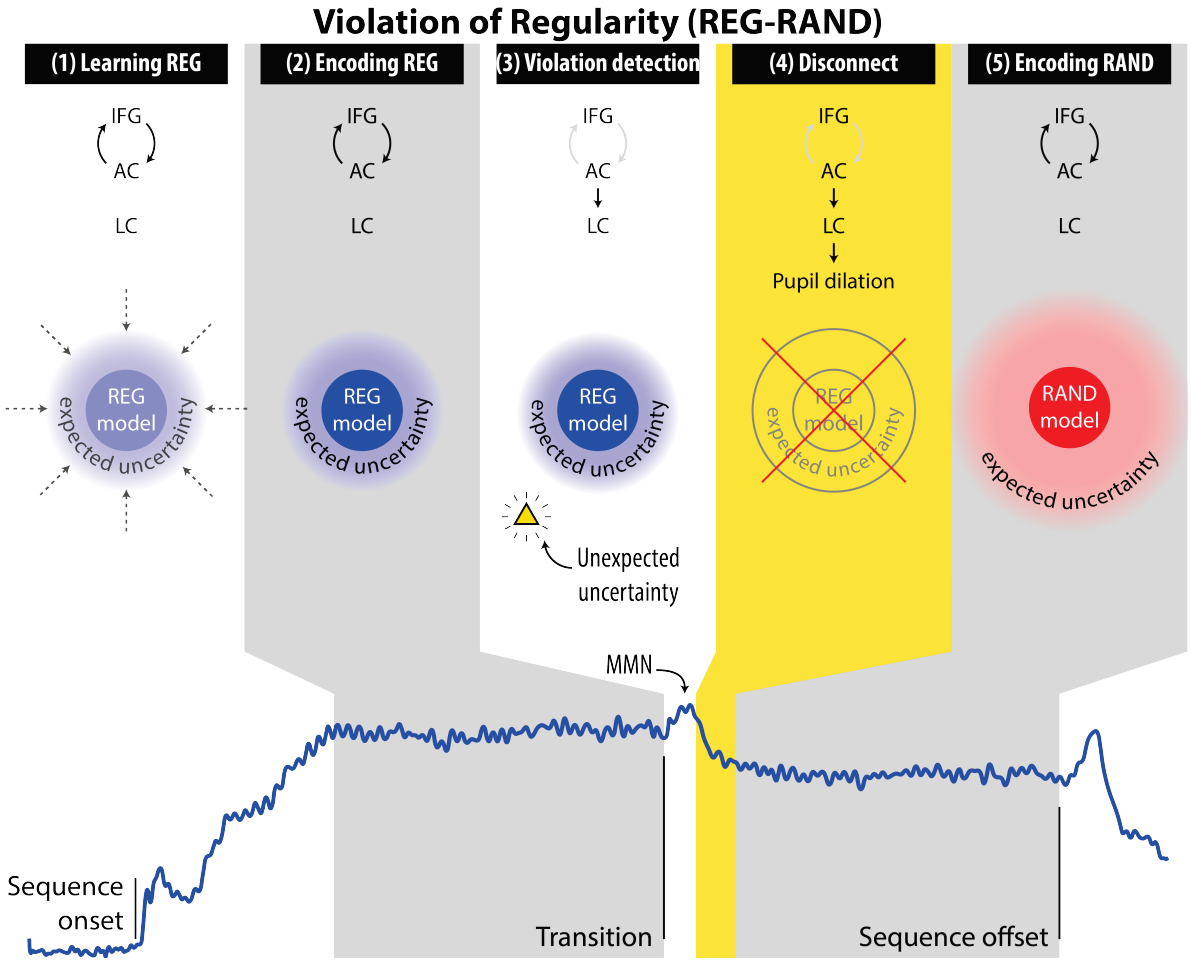


Figure 1.9 Hypothetical schematics for the processing of violations of regularity (REG-RAND).The MEG response for the sequence changing from a regular to a random pattern is plotted at the bottom (identical to that in Figure 1-6, adapted from Barascud et al. 2016). The entire process can be divided into (at least) five stages (indicated as five columns from left to right): (1) Starting from the sequence onset, the AC-IFG network gradually learns the statistics in the initial regular (REG) sequence, and continuously maintains the accuracy of the internal model (illustrated as a blue circle with small shaded surrounding area). (3) As the first tone of the new random pattern violates the regular pattern, this sensory signal fall outside of the existent model (indicated as a yellow triangle), and thus is an unexpected uncertainty. It is detected by the AC-IFG network, evoking an MMN component in the cortical response (as highlighted in the MEG result at the bottom of this figure). (4) The AC then conveys the appearance of this unexpected uncertainty to the subcortical LC, which in turn evokes a phasic NE response to deliver an interrupt signal to the rest of the brain, indicating the occurrence of a fundamental change in the sensory signal and initiating the disconnect from the existent internal model. The phasic NE response then causes an observable transient pupil dilation response. (5) The AC-IFG network continues learning and forming the new model for the RAND pattern (illustrated as a solid red circle with large shaded area).

1.6 Outline of this thesis

This thesis includes a series of seven human pupillometry experiments, in which the neural activity in the LC was indexed by changes in participants' pupil sizes while listening to these stimuli. If the NE system does operate over rapid timescales, then pupil dilation – and NE release – would occur after hearing transitions from regular to random patterns (REG-RAND) but exhibit no response to transitions from random to regular patterns (RAND-REG).

Chapter 2 provides a detailed overview of the pupillometry paradigm used in all seven experiments of this thesis. It opens with a brief review of cognition-related pupillary responses, including selected anatomical and physiological background on how pupil size changes, how the measurement of pupil diameter is conducted, and importantly, the major methodological challenges that must be considered when designing, collecting and interpreting pupillometric data. Following this, the experimental design is detailed, with a focus on how the measurement, analysis and presentation of pupil responses in the present study. Furthermore, a discussion on the limitations of standard pupil diameter analysis techniques introduces a new analysis method to provide complementary information about the evoked pupil responses.

The data collected from all seven experiments are presented and discussed in the chapters that follow (Chapters 3 to 7).

Chapter 3 presents pupillometric data from the first experiment, where pupillary responses to the rapid complex sequences described previously are measured, with participants not actively tracking the changes but instead performing a change-irrelevant task. The task used here is an auditory gap detection task, in which participants must continuously monitor the sequences and detect incidental silent gaps embedded within; occurrences of silent gaps are irrelevant to the changes. The purpose of this task is to maintain subject alertness and ensure the participants listen to the sequences without actively seeking and detecting the transitions. This chapter is devoted to introducing this new paradigm for studying unexpected uncertainty, with a focus on examining the gap detection task.

Following this, a series of control experiments seek to verify these results, and examine and preclude several alternative explanations. **Chapter 4** thus focuses on pupillary responses to the violation of regularity (REG-RAND). The experiment detailed in Chapter 4 aims to verify that pupil responses evoked by the transitions were driven by pattern changes and not mere deviant detection.

Chapter 5 focuses on pupillary responses to the emergence of regularity (RAND-REG) and examines how the pupillary response is influenced by the complexity level of the emerging regularity.

Chapter 6 investigates whether and how behaviour affects the statistical tracking process. Unlike all the previous experiments in this thesis, the participants are asked to actively detect and report the transitions in the sequences.

Chapter 7 explores the effect of the tasks on the evoked pupil dilation responses. Like the gap detection task used previously, the tasks investigated in this chapter are all irrelevant to the transitions; three additional passive listening tasks are introduced, with attention directed to different modalities in each of the three (auditory, visual, or tactile).

Chapter 8 presents a general discussion examining the finding of this thesis. Outstanding and new questions raised by the findings of this series of experiments, and proposals for future work will also be detailed in the final chapter of this thesis.

2 General Methodology

2.1 Pupillometry

In the 1960s, the measurement of pupil diameter in psychology – in short, pupillometry – was established after the publication of three seminal studies (Hess and Polt, 1960, 1960; Kahneman and Beatty, 1966). Since then, this method has been employed as a useful tool to explore fluctuations in various higher-level cognitive processing systems. In the 1980s, advances in measurement technology fully automated continuous recordings of pupil diameter, further boosting interest in pupillometry; a literature search in Web of Science yields more than 5000 relevant papers published over the last 57 years (1960-2017).

2.1.1 Changes in pupil size: anatomy and physiology

Visual perception begins at the pupil: light's entryway into the eye. The iris mediates this ingress of light by varying the diameter of the pupil through balancing interactions between the dilator (sympathetic, noradrenergic; mydriasis, meaning pupil dilation) and the sphincter (parasympathetic, cholinergic; miosis, meaning pupil constriction) muscles (Figure 2.1).

The primary objectives of regulating pupil size are to respond to changes in illumination (Loewenfeld and Lowenstein, 1993) and to attain maximum visual acuity during accommodation (Loewenfeld and Lowenstein, 1993). The first task – also known as the pupillary light reflex (Loewenfeld and Lowenstein, 1993) – is well understood and believed to regulate the trade-off between sensitivity and sharpness for the optimization of image quality (Campbell and Gregory, 1960; Laughlin, 1992).

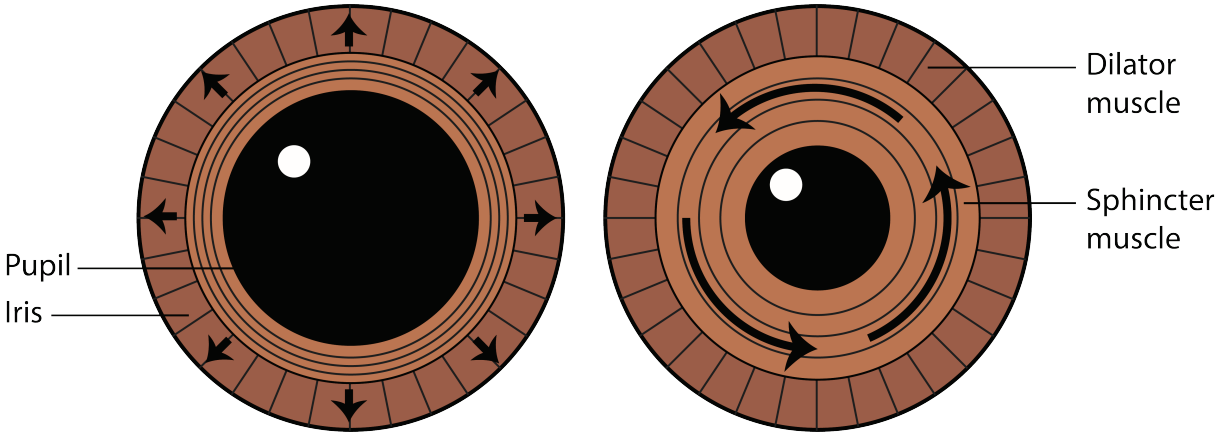


Figure 2.1 Dilator and Sphincter muscles within the iris. The dilator muscle (also known as radial muscle) receives noradrenergic input (NE) from the sympathetic nervous system, and the sphincter muscle (also known as the circular muscle) receives cholinergic input (ACh) from the parasympathetic nervous system. The balance between the activation of the dilator and sphincter muscles control the changes in pupil size.

There are other fluctuations of pupil size which do not serve those primary purposes; while there is no apparent purpose to these tiny changes, small enough to have no visual impact, they appear to correlate with cognitive and mental factors, including arousal (Bradley et al., 2008; Hess and Polt, 1960; Libby et al., 1973; Murphy et al., 2011), information processing load (e.g. Hess and Polt, 1960; Hoeks and Levelt, 1993; Kahneman and Beatty, 1966; Klingner et al., 2011), decision-making (e.g. de Gee et al., 2014; Einhäuser et al., 2010, 2008) and memory (Goldinger and Papesh, 2012; Naber et al., 2013) amongst others (Einhäuser, 2017; Laeng et al., 2012). As such, the underlying common neural circuitry linking these cognitive functions and their influence on pupil size is an area of intense interest. Although the neural substrate mediating these cognition-related pupil dilations is not as well-known as the light reflex, the LC-NE system has been thought to be associated with the regulation of pupillary responses (Aston-Jones and Cohen, 2005; Joshi et al., 2016; Rajkowski et al., 1993; Samuels and Szabadi, 2008a, 2008b) (see Chapter 1).

The evoked cognition-related pupillary responses comprise of two components, the early and late components which account for the initial dilation and subsequent contraction phases respectively. The early component, lasting for under a second, is caused by the inhibition of the parasympathetic system resulting in the relaxing of pupillary contraction

muscles leading to mydriasis. Appearing after this, the late component is due to the activation of the sympathetic system which leads to contraction of the dilator muscles and thus causes miosis (Loewenfeld and Lowenstein, 1993; Steinhauer and Hakerem, 1992).

Typically, the pupil diameter varies between 1.5mm in bright light and 9mm in complete darkness (according to the most recent review, Eckstein et al., 2017). Compared to these luminance-based changes, cognition-related pupil dilations are tiny, normally less than 0.5mm (Beatty, 1982; Sirois and Brisson, 2014); nonetheless, this is usually measurable under constant luminance with modern eyetrackers.

2.1.2 Methodological challenges

In a similar manner to event-related brain potential responses, identifying and distinguishing event-related pupillary responses involves repetition of the event multiple times until signal-processing methods can raise the signal-to-noise ratio sufficiently for analysis. Dating back to the 1960s, pupillometry studies have suffered from low sampling rates (e.g. 1Hz achieved by photographing the eye once per second) and a small number of trials (generally under five trials per condition per participant) (e.g. Hess and Polt, 1960; Kahneman and Beatty, 1966). Presently, pupil responses can be measured inexpensively, conveniently and non-invasively by video-based eye-tracking with high temporal resolution and sampling rates (up to 2000Hz), and enhanced signal-to-noise ratios (e.g. tens of trials per condition).

Despite these advances, designing well-controlled studies to produce robust cognitive interpretations from pupillometry still requires overcoming various challenges (Holmqvist et al., 2011). The most significant of these is the light reflex as mentioned previously. Pupil diameter has a strong light dependency, and variations can result in pupil diameter changes by up to 50% (Loewenfeld and Lowenstein, 1993; Newman et al., 2008). Hence, the luminance of the stimuli and the ambient lighting of the experimental environment are factors which must be carefully controlled by employing isoluminant stimuli and ensuring static environmental illumination. Moreover, considering that the cognition-related pupil dilation is larger in moderate

light than in complete darkness (Steinhauer et al., 2004), it is recommended to conduct experiments in a moderately and constantly lit room.

Another confound is the effect of changes in gaze position on the pupillary image, also known as pupil foreshortening error. With a fixed eye tracking camera recording a spherical eye, if the eye rotates away from the centre, the recorded pupillary image would appear to become elliptical. This causes its area and diameter, from the camera's perspective, to shrink by as much as 10% (Hayes and Petrov, 2016); this is a significant effect, as cognitive effects rarely elicit pupil diameter changes of more than 5%. The customary technique uses eye fixation to avoid this, often achieved by instructing participants to continuously fixate their gaze at a fixation mark (SR research, 2010, p28). To help avoid pupil position changes caused by head movements, commercial eye-tracking systems (like those from Eyelink and Tobii) are accompanied by a chin-rest stand which helps participants to stabilise their head position.

Another issue to be addressed by experimental design is the prolonged stimulus duration and inter-trial interval (ITI). This is due to the relative slow evolution of the pupillary responses (e.g. Hayes and Petrov, 2016; Murphy et al., 2011). For the light reflex, the pupil can take up to 1.5 seconds to reach maximum constriction after a sudden flash (Loewenfeld and Lowenstein, 1993), and when tracking slow changes in luminance, the pupil responds with a lag of around one second (Yellin et al., 2015). In cognition-related pupillometry studies, the dynamics of the pupil response vary across studies depending on the nature and difficulty of the task. The fact that the peak pupillary response lags behind the stimulus by around one to two seconds necessitates longer baseline and stimulus durations. Additionally, as the resolution of the evoked pupil dilation is on the order of seconds, Hoeks and Levelt (1993) recommend an inter-trial interval of six to ten seconds to allow the pupil diameter return to the baseline. Hence, despite the facility to measure pupil diameters at the sub-millisecond time scale, most studies still employ relatively slow stimulation with a relatively large separation between stimuli.

Apart from these task-related confounds, there are also a variety of participant-related confounds that researchers must be aware of. For example, baseline pupil diameters change with age, which are correlated with changes in cerebral levels of NE (Herlenius and Lagercrantz, 2001). According to the Eckstein et al.'s review on eyetracking (Eckstein et al., 2017), pupil diameter (measured in dim light) increases rapidly from 5.5 mm in 1-month olds to 7mm in 10-year olds, plateaus around 7.5 mm at the age of 11-15 years, and then slowly but persistently shrinks reaching around 4.5 mm in 80-year olds (Loewenfeld and Lowenstein, 1993; MacLachlan and Howland, 2002). Thus, it is also important to ensure participants have similar ages.

In addition to age, pupil diameter is also affected, for example, by wakefulness, anxiety level, and use of pharmacological agents that affect NE levels (e.g. caffeine, marijuana). Thus, in the present study, before testing, participants were reminded to ensure good rest, asked if they have taken any medication recently, and provided with a friendly testing environment to help reduce anxiety.

These methodological confounds have been carefully considered and handled in the present study. Subsequent sections of this chapter describe the general experimental design common throughout all six experiments, explaining the collection and analysis of pupil data. Any differences within individual experiments are highlighted in dedicated sections of the Data chapter.

2.2 Apparatus and procedure

2.2.1 Participants

The experimental procedures were approved by the Research Ethics Committee of University College London. Participants were provided written informed consent and were paid for their participation. All reported normal hearing, normal or corrected-to-normal vision, and no history of neurological disorders.

2.2.2 Stimuli

Since this thesis focuses at the pupillary responses to the transitions, it is important that there is sufficient time between sequence onset and the transition, and between the transition and sequence offset to allow the relatively slow evolution of the pupillary responses to fully develop. Therefore, the sequences were 5 to 7 seconds long (between 100 and 140 tones) with the transition time varied randomly between 2.5–3.5 seconds after sequence onset, ensuring that the post-transition sequence was least two seconds long. Both pre- and post-transition sequence lengths were longer than those in the previous MEG study (Barascud et al., 2016).

In Experiment 1, results showed that the evoked pupillary response needed more than two seconds to resolve. Thus, all subsequent experiments extend the post-transition sequence by one second, producing a sequence length of between 6–7.5 seconds and a post-transition sequence was of at least three seconds long.

2.2.3 Procedure

Participants sat in front of a monitor at a viewing distance of 60cm in a dimly lit and acoustically shielded room (IAC triple walled sound-attenuating booth), with their head fixed on a chinrest. Before starting the experiment, participants adjusted the table height for comfort using electronic controls.

Pupil responses were recorded while presenting auditory stimuli diotically through the headphones. The details of the tasks and stimuli featuring in each experiment are explained in each experiments' respective sections.

Participants were instructed to continuously fixate at a persistent white cross presented at the centre of the screen against a black background. The visual display remained the same throughout. To avoid confounding effects from the pupillary light reflex, the luminance of the screen and the ambient illuminance of the experimental room were kept constant throughout the experiment.

Participants were instructed to respond – by pressing a keyboard button – as quickly as possible after detecting the target (varies based on the task, for details see each experiments' section). Visual feedback was provided at the end of each sequence and displayed for 400ms at the centre of the screen, with a green tick indicating correct responses and a red cross indicating incorrect responses. Trials in which participants missed a response or responded with a false positive were excluded from analysis.

Stimuli were presented in a randomised order with an inter-trial interval (ITI) of five to seven seconds, sufficient to allow the pupil dilation to resolve after each trial (Hoeks and Levelt, 1993).

To reduce fatigue, stimuli were presented in blocks limited to eight minutes in length and participants were asked to take a short break of around three to eight minutes after each block.

Prior experimental experience has shown that experiments should not exceed one hour in length to ensure smooth, high-quality pupillometry data collection and avoid the loss of data through the fatigue-induced increase in blink rate, and the need to rouse and confirm the wakefulness of participants. In this thesis, Experiments 1, 5 and 7 contain four consecutive blocks, for a total of approximately 45 minutes (including instruction and breaks). However, the other four experiments contain more stimulus conditions, requiring more than 60 minutes to complete if running blocks consecutively. Hence, to reduce fatigue, participants were asked to rest longer between blocks: In order to efficiently use the experimental facilities during these extended breaks, two participants were interleaved between blocks: one rested while the other completed the block. Therefore, participants typically had over 10 minutes rest between blocks, extending the overall experimental session to just below three hours.

2.2.4 Pupil size measurement

An infrared eye-tracking camera (Eyelink 1000 Desktop Mount, SR Research Ltd.), positioned just below the monitor, continuously tracked gaze positions and recorded pupil

diameters, focusing binocularly at a sampling rate of 1000 Hz. The standard five-point calibration procedure for the Eyelink system was conducted prior to each experimental block, and participants were instructed to avoid any head movement after calibration. A 24 inch monitor (BENQ XL2420T) with resolution of 1920x1080 pixels and a refresh rate of 60 Hz presented the fixation cross and feedback.

Blocks were started by the participants themselves by pressing a keyboard button to indicate their readiness; this was followed by a 10 second pause before the presentation of auditory sequences.

Participants were instructed to blink naturally during the experiment. They were also encouraged to rest their eyes briefly during inter-trial intervals. Prior to each trial, the eye-tracker automatically checked that the participants' eyes were open and fixated appropriately; trials would not start unless this was confirmed.

2.3 Pupil size analysis

2.3.1 Pre-processing

Choosing eye

Since pupillary responses are correlated across both eyes (see review Wade and Tatler, 2011, and see the example in Figure 2.2), by default, only the left eye was analysed, unless there was missing data, for example due to the camera angle or the participant's eye shape.

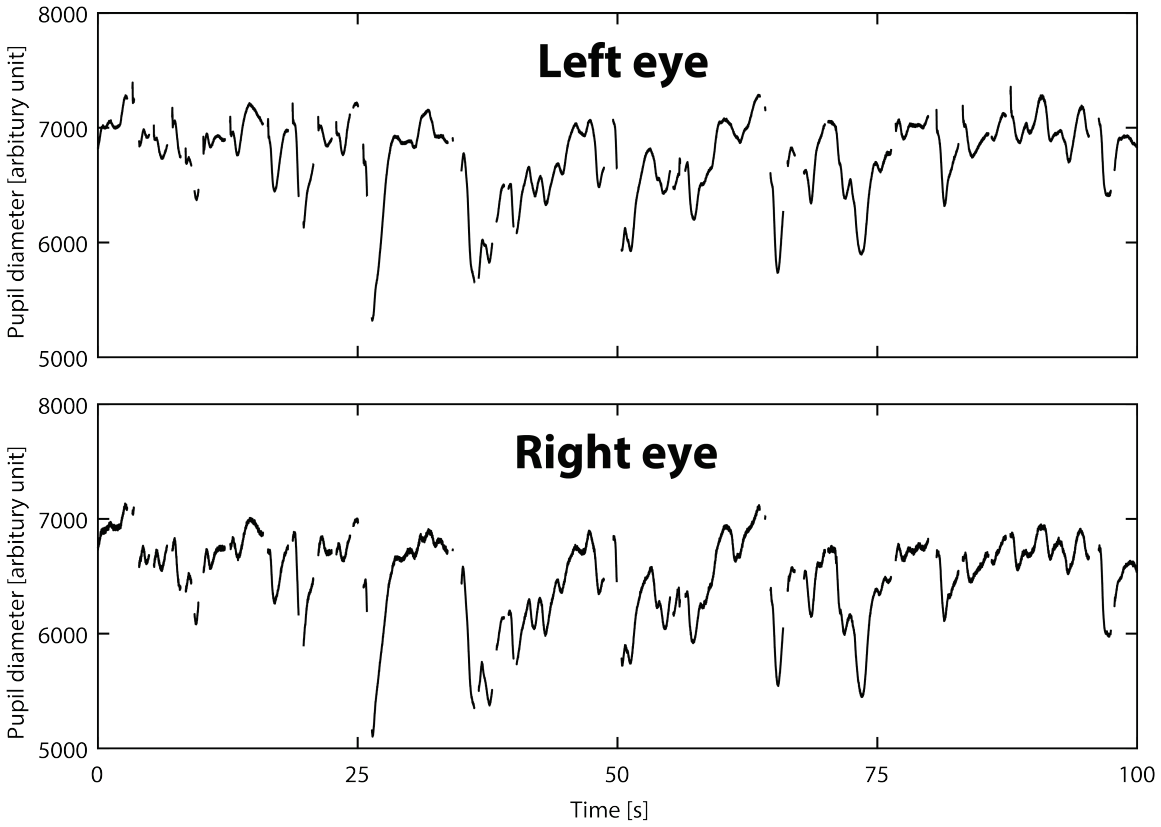


Figure 2.2 The consensual nature of pupillary responses. Example of continuous pupil data from both eyes are presented on the top (left eye) and bottom (right eye) panels. This 100 second interval is taken from Subject S1's first block from Experiment 1B. Blinks have been treated as missing data, shown as breaks in this figure.

Epoching

To measure pupil dilation responses evoked by transitions in STEP, REG-RAND and RAND-REG signals, the pupil data of each trial were epoched from one second before the transition through to the offset of the sequence.

Excessive blinks or any stimulus-related changes in blink rate can cause confounds which complicate the interpretation of the results. Thus, the rate of blink occurrence as a function of time relative to the transition time was examined to explore these effects. Taking Experiment 1A as an example, the average blink rate (Figure 2.3A) starts to increase when approaching the stimulus offset. Thus, pupil diameter data was truncated to two seconds (Experiment 1) or three seconds (all other experiments) post-transition. This cutoff is comfortably beyond the time needed to detect the transitions, corroborated by behavioural

(see Barascud et al., 2016, and behavioural results in the following chapter) and MEG (Figure 1.6, Barascud et al., 2016) results.

Non-transition conditions (CONST, REG, and RAND) were epoched in a similar manner but using 'dummy' transition times: the time at which a transition would have occurred in their associated transition condition.

Normalisation and Baseline correction

The EyeLink 1000 system records pupil diameters in arbitrary units in the range of 400 to 16000 units, at a precision of 1 unit, which translates to a range of 3–9mm, accounting for participants' individual differences (Hayes and Petrov, 2016). According to the EyeLink 1000 User Manual (SR research, 2010), this arbitrary unit is uncalibrated and susceptible to influence from the tracking set-up and calibration at the beginning of each block. Thus, to compare the results across blocks, conditions and participants, the pupil data during epochs within each block were normalized to z-score by:

$$P = P - \frac{\overline{P}}{\sigma_P} \tag{1}$$

where P is all epoched pupil data within the block, $\overline{P}$ and σ_P are the mean and standard deviation of P respectively.

A baseline correction was then applied by subtracting the median pupil size of the pre-transition baseline. The median is a common choice for pupil data to avoid the undesirable contributions of outliers.

Smoothing

The data were smoothed with a 150ms Hanning window (see Figure 2.5A for the effect of smoothing).

Blink removal

Intervals where the eye tracker detected full eye closure were automatically treated as missing data (Figure 2.5A). Trials with more than 50% missing from the epoch were excluded from analysis. Across all experiments, on average each participant had less than two rejected trial. Data from participants with excessive blink rates (see *Participant exclusion criteria* for details) were omitted from the analysis.

In addition to these full eye blinks, partial eye closures were also treated as missing data. These are characterised by a rapid drop by more than 1 z-score of pupil diameter, followed by a rapid rise back to a pre-closure value within 500ms (arbitrarily selected by visual inspection); these events were located by the MATLAB function 'findpeaks'. The missing data (including 150ms before and after) were recovered with shape-preserving piecewise cubic interpolation (see Figure 2.3B for an example of a half-blink and the resulting reconstructed data).

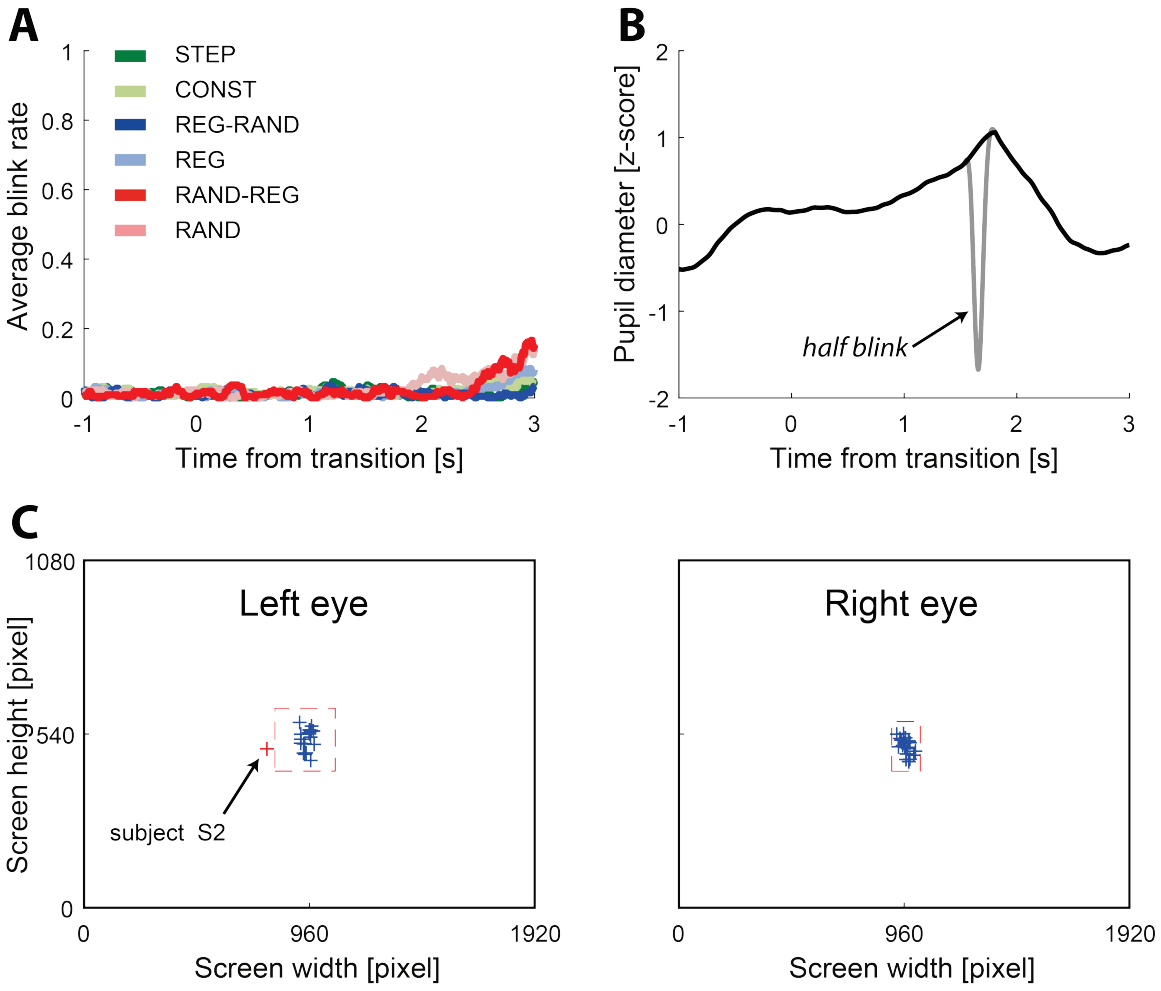


Figure 2.3 Pre-processing for pupil diameter. [A] Average blink rate (example from Experiment 1B). Solid lines with different colours represent average blink rate for each condition. Blink rates for all conditions start to increase towards stimulus offset. [B] Half-blink removal. The grey curve shows the original data of a single trial, with a partial eye closure (also called 'half blink'), and the black curve shows the cleaned result after blink removal and interpolation. [C] Gaze location for participant exclusion. Blue crosses indicate the mean gaze locations for each participant, and the dashed red rectangle represents three standard deviations from the group mean. Participants are excluded if the mean gaze location of one of their eyes lies beyond this rectangle. In this example, (Experiment 2) the left eye of one subject (Subject S2) exceeded the threshold (indicated as a red cross in the left plot); they were therefore excluded from any further analysis.

2.3.2 Participant exclusion criteria

Liao et al. (2016) showed in a pupillometry study on auditory oddball detection that changes in the auditory sequence may affect blinking. Therefore, to ensure that observed changes in pupil diameter are not blink-related artefacts, participants were excluded if they blinked in more than 50% of trials at any given time for each condition.

Additionally, gaze position can affect the accuracy and effectiveness of the eye tracking system. Although the gaze location was checked prior to every trial, and participants were explicitly instructed to fixate on the white cross at the centre of the screen, to further reduce artefacts caused by eye movements (Brisson et al., 2013; Hayes and Petrov, 2016), participants are excluded if their mean gaze location exceeded three standard deviations from the group mean (Figure 2.3C).

These exclusion criteria were consistently applied across all experiments.

2.4 Plots

2.4.1 Across-trial averaging of pupil diameter

To characterize the pupillary response to different stimulus conditions, the eye tracking recording was segmented into epochs as discussed above, and time-domain averaged across all epochs of each condition type, to produce a single time series for each condition describing the average pupil diameter as a function of time. This assumes that event-related pupil responses are stationary with similar forms and latency, while other non-pertinent non-event-related responses are randomly spread. From this, non-event responses are greatly diminished by the averaging process, and thus augmenting the signal-to-noise ratio of the event-related responses.

Time-series statistical testing

To search for differences between the pupillary responses to the transitions and their controls, we used cluster-based permutation statistical testing which is commonly used to examine differences in EEG and MEG brain potentials (Guthrie and Buchwald, 1991; Maris and Oostenveld, 2007) as it avoids the complications caused by multiple comparisons; recently this technique has been introduced to pupillometry (e.g. Privitera et al., 2010; Siegle et al., 2004). To control the family-wise error rate, this test involves repeated resampling the grand mean pupil diameter from all subjects with 5,000 iterations, and for every time sample over the length of the epoch, computing t-values between the transition condition and its control. Then, all time samples whose t-value passes the threshold (e.g. $p<0.05$ used in the present study) were selected and clustered in connected sets based on temporal adjacency. The sum of the sample-specific t-statistics that belong to this cluster is taken as a cluster-level statistic and is then used to determine the significance of the clusters. To save processing time, the pupil data were downsampled to 20Hz before the comparison. The cluster defining height threshold was $p<0.05$ and the family-wise error corrected cluster size threshold was $p<0.05$, as implemented in Fieldtrip (www.fieldtriptoolbox.org, Oostenveld et al., 2010). Time intervals with significance are presented as coloured horizontal bars below the respective average pupil diameter plots.

Limitation of across-trial averaging

Obtaining a reliable estimate of the temporal evolution of the pupil diameter requires the across-trial averaging of pupil data epochs: a common method to evaluate the event-related phasic pupil dilation response, as featured in a wealth of pupillometry studies (e.g. Kahneman and Beatty, 1966; Liao et al., 2016; Privitera et al., 2010). However, not unlike the issues encountered in the analysis of event-related potentials (Mouraux and Iannetti, 2008), this technique may adversely affect responses if they are not temporally aligned across trials. The problem worsens when latencies are greatly jittered, resulting in depressed amplitudes due to temporal spread, and in extreme cases, even complete concealment of responses if the jittering is sufficiently wide (see Srinivasan, 2005). For example, an absence of change when

employing time-domain averaging does not necessarily mean that there was no pupillary response, but merely that pupil dilations occurred with a significant latency jitter pattern. Fortunately, since pupillary responses are relatively slow and sustained, moderate latency jitters (on the order of hundreds of milliseconds) should not substantially affect the observed pupil dilation response.

Nevertheless, there is a wealth of unexplored information that could be gleamed by looking at the pupil dilation (or constriction) events at a single trial level, the detail of which may be lost by collapsing the data from many trials into one waveform. Importantly, as shown in works on the correlation between pupil dynamics and LC neural activity, the timing of the phasic LC response is strongly correlated with the onset of pupil dilation, hence it is important to carefully examine pupil dilation and constriction events, as they potentially provide much tighter links with the dynamics of the LC-NE system.

As shown by the results of the following chapters, pupil dilation (or constriction) rate analysis is valuable technique for exploring pupillometry data and can even provide complementary information such as the latency jitter of pupillary response events on a trial-by-trial basis.

As mentioned before, each cognition-related pupillary response comprises of two components: pupil dilation and the following constriction. Although these two components are normally tightly coupled, it is unclear whether the dynamics of these two components – for example, latency – are identical across trials. Here, this event-based analysis allows the dissociation of pupil dilation and constriction events, which may provide interesting insights that the standard across-trial averaging of pupil diameter obscures.

Thus, the present study proposes a new pupillary response analysis – pupil dilation/constriction rate analysis – which focuses on the latency of the events on a trial-by-trial basis and provides an opportunity to look at the two components, pupil dilation and constrictions, separately.

2.4.2 A new analysis technique: pupil event rate analysis

Define and detect pupil dilation/constriction events

Pupil event rate analysis compares the incidence of pupil dilation or constriction events at a single-trial level. The first step of this analysis is to extract events from the continuous pupil data (see Figure 2.5B). A pupil dilation (PD) event is defined as an interval in which the pupil diameter increases continuously (see Figure 2.4 for a schematic of a pupil dilation response, see also Beatty and Lucero-Wagoner, 2000; Wang et al., 2014), and a pupil constriction (PC) event is defined as a continuous decrease. The onsets of pupil dilation events are identified as the local minimum or the instantaneous positive sign change of the pupil diameter derivative, while the onsets of pupil constriction events are defined as the local maximum or the instantaneous negative sign change of the pupil diameter derivative (Figure 2.5B).

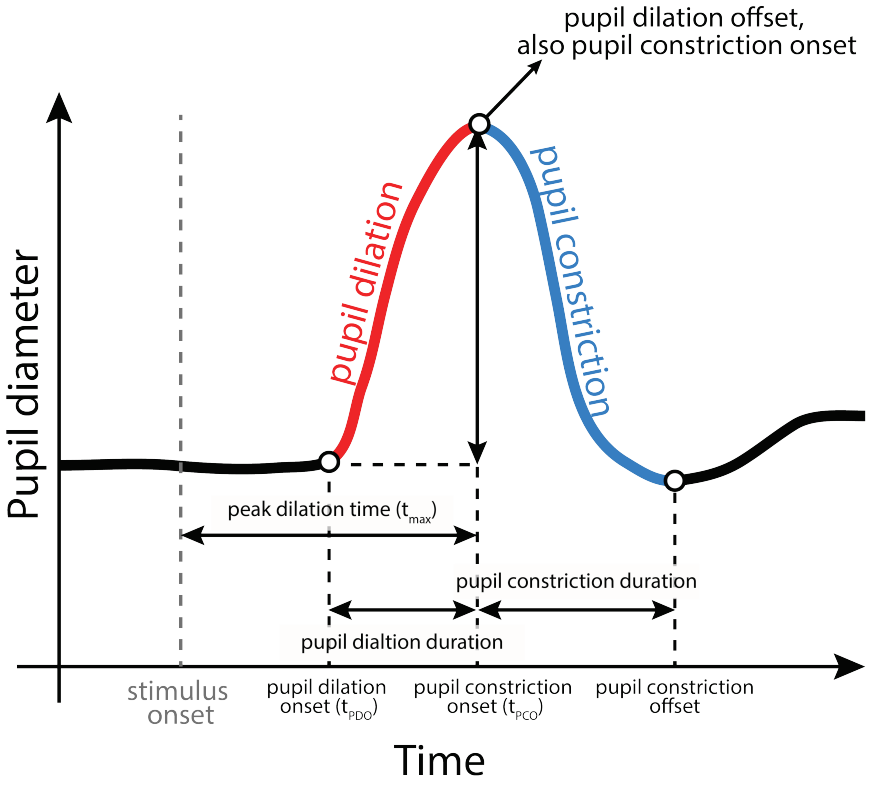


Figure 2.4 Schematic diagram of measurements of an evoked pupil dilation response.

To reduce noise caused by momentary amplitude flutters, a temporal threshold was applied to pupil events; for example, applying a 75ms threshold means that only intervals where the pupil diameter continuously grows or shrinks for more than 75ms are considered to be pupil dilation or constriction events. The threshold 75ms was previously used in a monkey pupillometry study to extract pupil dilation events (Joshi et al., 2016). To demonstrate the stability of this methodology, data are presented with two threshold values, 75ms and 300ms, multiples of the Hanning window length (150ms) used for data smoothing. Justification for these two threshold values can be seen in the duration distribution of pupil dilation and constriction events (Figure 2.5). Figure 2.5C presents the distributions of pupil dilation durations (median 350ms, peak 75ms) and pupil constriction durations (median 250ms, peak 75ms). As shown in the results section of the next chapter (Chapter 3), both thresholds provide consistent data, as do intermediate thresholds (including 100ms and 125ms; these results are not shown as they show very close consistency).

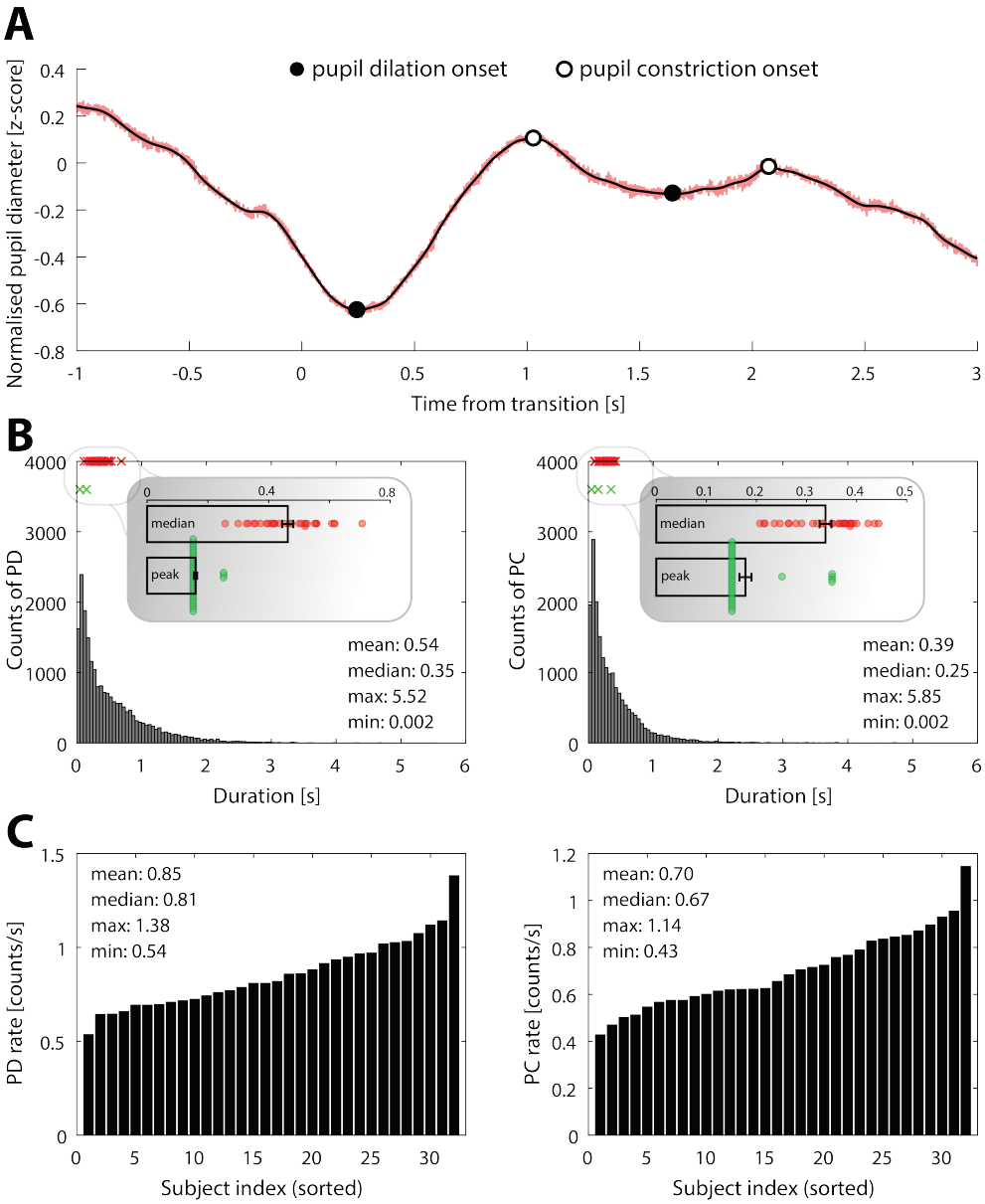


Figure 2.5 Pupil event rate analysis. [A] Effect of smoothing on an example single trial of pupil diameter. The red curve represents normalized, baseline-corrected and pre-smoothing data, and the black curve shows the data after smoothing with a 150ms Hanning window. Filled and open circles indicate local maxima and minima respectively, which define pupil 'events'. Namely, filled circles indicate the onset of pupil dilation, and open circles indicate the onset of pupil constriction. [B] Distributions of pupil event durations for all subjects and all blocks in Experiment 1. Dilation duration is defined as the interval between local minima and their subsequent maxima, while constriction is the interval between local maxima and subsequent minima (cf. Joshi et al., 2016 for monkey pupillometry). Median values for each subject (N=32) are presented as red crosses above the histogram, and peak values for each subject are presented as green crosses. For clearer display, median and peak values for each subject are shown in the bar plot next to the histogram. The peak value is computed by finding the tallest bin in each subject's histogram (with a bin width 0.1s between 0 to 6s). Each subject's histograms of pupil dilation and constriction durations are plotted in Figure 2.6 and Figure 2.7 respectively. [C] Number of pupil events per second during the pre-transition interval for all subjects (N=32), with a threshold of 75ms. Subject index (x-axis) is sorted by event rate. Typically, one pupil dilation/constriction event occurs every one to two seconds in the pre-transition interval in Experiment 1.

Computation of the incidence rate of pupil dilations/constrictions

Once these events are extracted, the incidence rate of pupil dilations and constrictions can be computed. There are many ways to do this: one way is to convolve these events with impulse functions, paralleling a similar technique for computing neural firing rates from neuronal spike trains (Dayan and Abbott, 2001). This has been effectively employed in previous works including Joshi et al. (2016) on monkey pupil dilation and constriction, Rolfs et al. (2008) on microsaccades, and another work of the present study's author (not featured in this thesis). Another way, as applied in the present study, divides the data into non-overlapping temporal windows (e.g. 500ms), then counts the number of events within each window and divides this by the number of trials and the length of the window. For example, with 500 trials from all subjects and 375 pupil dilations within a 500ms window, the pupil dilation rate in this interval is 1.5 events per second. This study deliberately chose the latter method because it provides maximum sensitivity to subtle increases in the pupil event rate – an absence of a pupil dilation response in the archetypal across-trial average analysis could be due to a small increase in the event rate. In conjunction with the wide 500ms window, this method allows the capture of pupil events even if they are not time-locked and exhibit significant latency jitter (see *Results* of the next chapter for a discussion).

The main caveat of this event-based analysis is that it requires many trials to compute the incidence rate; from the results of two additional auditory studies – carried out in parallel with the present study and also employing this technique – at least 500 trials are required to obtain reliable estimates of the rate. This is solely due to the relative sparsity of pupil dilation and constriction events; in the present study, there are typically only 0.85 pupil dilations and 0.70 pupil constrictions per second during the pre-transition portion of the stimulus (based on the data from Experiment 1, Figure 2.5D). Currently, it remains unclear how pupil dilation and constriction rates are affected by experimental factors, such as the nature of the stimuli and the task that subjects are performing; this requires further study and investigation. As shown in the following chapters, this pupil event rate analysis can provide novel and interesting

insights on the dynamics of pupillary responses, raising the possibility that further understanding of the mechanics of pupil event rates would in turn benefit studies about the precise mechanism behind cognition-related pupillary responses and its relationship with the LC-NE system.

3 The pupil dilates to violation but not emergence of regularity

3.1 Motivation

Brain imaging works have shown that listeners are very sensitive to unexpected pattern changes in rapid complex sound sequences, so much that these changes can be rapidly detected even without direct attention (Barascud et al., 2016). The present study employs the stimuli described in Chapter 1 to investigate two questions about the role of the LC-NE system: Firstly, is the phasic NE response sensitive to changes embedded in rapidly changing acoustic signals? Secondly, does this response require listeners to be actively seeking and reporting the changes?

Based on previous literature, it can be expected that abrupt pattern changes in these rapid sound sequences activate the NE system and trigger phasic NE activity. However, not all types of pattern changes should activate the NE system; phasic LC activity should be selective to changes associated with unexpected uncertainty, such as deviant detection (like the STEP transition) and transitions from regular to random patterns (REG-RAND). Thus, the transition from random to regular (RAND-REG) which leads to an increase in precision should not trigger any phasic NE response. As the transitions STEP and REG-RAND convey fundamental changes in the sensory signal, detection of this change should initiate a functional reset to communicate that the external environment has changed, and that prevailing internal representations are no longer valid and must be updated. As reviewed in Chapter 1 (Bouret and Sara, 2005; Dayan and Yu, 2006; Yu and Dayan, 2005), the unexpected uncertainty theory

proposes that this process should be signalled by phasic NE responses, which can be observed as transient pupil dilations. Thus, transient pupil dilation responses should be observed following the STEP and REG-RAND transitions, but not after RAND-REG.

Furthermore, this NE response may be perception-driven and not require behavioural relevance, or in other words, this pattern-change evoked pupil dilation response should remain robust even when participants are *not* voluntarily detecting the changes. This possibility arises from a previous study (Barascud et al., 2016) that has shown that these pattern changes can be automatically and rapidly detected by naïve listeners, even when distracted by an incidental and irrelevant visual task, which presented participants with groups of three photographs and required them to report if the third photograph is identical to the two presented before.

However, the visual task of the previous MEG study is not appropriate for the present pupillometry study, as the presentation of imagery would inappropriately and strongly affect pupillometric measurements and involve further confounding factors. A task suitable for the present study should satisfy two conditions: First, the target of the task should be irrelevant to the pattern transition in the stimuli. Participants should not make any decisions about the transition, as the decision-making process might confound pupil responses to the transitions. Secondly, it should ensure that participants maintain alertness to the experimental stimuli. Thus, to fulfil these requirements, a new auditory gap detection task was developed. In this, listeners are instructed to report occasional brief gaps in the sound sequences. As the position of gaps occur independently to the transitions, this would ensure that participants are not making decisions about the transition itself, thus eschewing the confounding effects of decision-making processes. As the gaps appear very rarely, all trials which include a gap or received a response can be removed from the further analysis.

3.2 Experiment 1A

3.2.1 Methods

Participants

Data from 18 participants (11 females; aged 20–29, average 23.41) are presented. Data from one additional participant was excluded due to failure to complete the experiment. Two further participants were excluded due to high blink rates in the STEP condition.

Stimuli

The basic stimuli used in the present study are illustrated in Figure 3.1 and adapted from those used in Barascud et al. (2016), as described and reviewed in Chapter 1. The six stimulus conditions were the three transition stimuli (STEP, REG-RAND and RAND-REG) and their corresponding no-change controls (CONST, REG and RAND). The stimulus length varied randomly between 5 and 7 seconds, with a jittered transition time at around 2.5 and 3.5 seconds post-onset.

It is important to note the alphabet size of RAND is 20 – that is, the RAND sequence is constructed by sampling from all 20 frequencies in the pool – while REG is deliberately limited to 10. This is because previous behavioural results (Barascud et al., 2016) have established that, while emergences of regularities with a size of 10 tones can be detected as fast as an ideal observer (reviewed in Chapter 1), further extending the alphabet size of the regular pattern to 20 tones results in a significant detection time lag, with typical responses falling nine tones behind an ideal model. This indicates that efficient detection rapidly deteriorates as cycles exceed 10 tones, most likely due to deficiencies in memory retention and capacity. Thus, as to exploit maximal complexity without invoking memory limitations, the length of regular patterns was fixed at a maximum length of ten tones, or 500ms.

According to the behavioural and MEG results of Barascud et al. (2016), the three transitions – STEP, REG-RAND and RAND-REG – should all be detectable; STEP and REG-RAND are detectable immediately after transition, as the first tone after transition violates the

preceding pattern, whilst RAND-REG should require a half-cycle of the regular pattern. As the regular cycles here are 10 tones long, detection of the RAND-REG transition should require an extra four tones (200ms) compared to REG-RAND. Chapter 6 also provides confirmation of this.

In this paradigm, one-sixth of the sequences contained a gap partway through the sequence, and participants were instructed to monitor for these gaps. This assured broad attention to the auditory modality while maintaining orthogonality to the transitions within the sequences. The timing of the gap varied and could occur at any time from 250ms post-onset to 750ms pre-offset. Additionally, to equate for task difficulty, the gap consisted of one missing tone (50ms) in the CONST and STEP sequences, and two missing tones (100ms) in REG and RAND sequences.

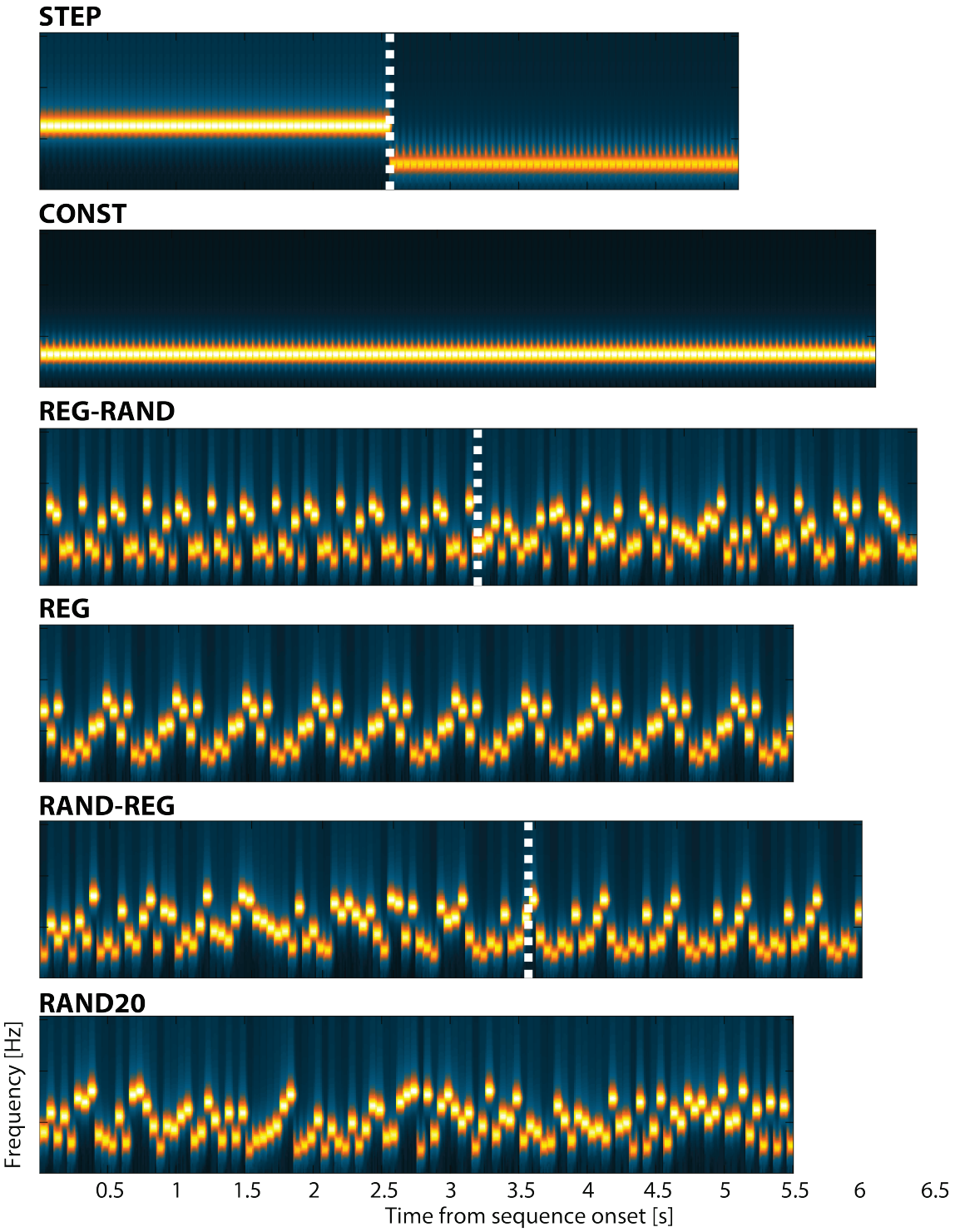


Figure 3.1 Example spectrograms of stimuli used in the present study. The three transition conditions are presented in pair with their corresponding controls (Top to bottom: STEP, CONST, REG-RAND, REG, RAND-REG and RAND). Transition times are indicated with a white dashed line. The transition in RAND-REG only becomes statistically detectable once the pattern begins to repeat, i.e. not before the first full regularity cycle has been presented. Therefore, that point is considered to be the transition time for RAND-REG signals. All stimuli were generated anew for each subject.

Procedure

As reviewed in Chapter 1, low probability of stimulus presentation can affect pupil responses, thus, to avoid possible confounds due to differing appearance probabilities of the transition stimuli, experimental sessions contained equal proportions of trials with and without changes, and equal proportions of each pair of transition stimuli. In the present experiment, 146 stimuli – 24 each of CONST, STEP, REG, 20 REG-RAND, RAND, RAND-REG – were presented in four consecutive blocks, all randomly shuffled, and with an inter-trial interval of six seconds. Participants were asked to take a short break of around three minutes between blocks.

In this experiment, participants responded to a gap by pressing a keyboard button as quickly as possible once detected. Within each block, six trials contained a gap, comprising of one of each stimuli type. Visual feedback, lasting 400ms, was provided immediately at the end of each sequence. Trials containing a gap, or trials in which participants' responses were incorrect, were excluded from further analysis. Thus, in this experiment, only 120 stimuli (comprising of 20 from each condition) out of 146 total stimuli were used for pupillary analysis.

All stimuli were generated anew for each participant and delivered to the participants' ears by Sennheiser HD558 headphones (Sennheiser, Germany) via a Creative Sound Blaster X-Fi sound card (Creative Technology, Ltd.) at a comfortable listening level, self-adjusted by each participant. Stimulus presentation and response recording were controlled with the Psychtoolbox package (Psychophysics Toolbox Version 3; Brainard, 1997) on MATLAB (The MathWorks, Inc.).

Note that this standard procedure as detailed thus far is applicable to all experiments in this thesis; any differences between the procedures described here and subsequent experiments will be detailed and explained in their corresponding sections.

3.2.2 Results

Average pupil diameter from stimulus transition

Figure 3.2A plots the average normalised pupil size across all participants as a function of time relative to the transition. Following the transition, clear pupil dilation responses are observed in the STEP and REG-RAND conditions. The pupil diameter in STEP starts to increase around 300ms post-transition and peaks at 1520ms, statistically diverging from its control CONST from 560ms through to sequence offset. Similarly, the response to REG-RAND increases from around 700ms post-transition, and then peaks at 1640ms. REG-RAND statistically diverges from its control REG at 1000ms post-transition and continues until 2400ms. No significant difference between RAND-REG and RAND can be observed. When comparing the transition conditions with each other, there is no significant difference between the STEP and REG-RAND conditions; but comparing the responses of REG-RAND and RAND-REG, we found that RAND-REG is significantly lower from REG-RAND from 840ms post-transition until stimulus offset.

This result shows that the STEP and REG-RAND transitions can evoke transient pupil dilations, while the RAND-REG transition does not appear to elicit any observable change in average pupil diameter.

Behavioural results

Hit rates for the gap detection task are shown in Figure 3.2B. Overall, while the performance is similar for CONST and REG, the mean hit rate is lower for RAND. A repeated measures ANOVA confirms a main effect of condition ($F(1.198,20.372)=8.285$, $p=0.007$, with Greenhouse-Geiser correction as Mauchy's Test of Sphericity indicates a violation of the assumption of sphericity). The hit rate in RAND is significantly lower than CONST ($p=0.026$) and REG ($p=0.026$), while CONST and REG do not differ significantly ($p=1.000$; Bonferroni corrected). Moreover, repeated measures ANOVA shows no effect of condition on false positive rates ($F(1.312,22.298)=1.528$, $p=0.235$, with Greenhouse-Geiser correction as

Mauchy's Test of Sphericity indicates a violation of the assumption of sphericity), which were all very low (CONST=1.1±1.1%, REG=3.3±1.3%, RAND=2.5±1.2%).

There is the possibility that the higher task difficulty of RAND may be a confounding factor in the null-effect of RAND-REG. Differences in task difficulty across conditions results in a difference in cognitive processing load, and possibly drives participants to implicitly devote different amounts of attention to different conditions. As mentioned before, these two factors – cognitive processing load and attention – have the potential to significantly affect cognition-related pupil dilations (Beatty, 1982; Hess and Polt, 1964; Kahneman et al., 1967). Thus, the next experiment, Experiment 1B, controls task difficulty to remove the possibility that variations in task difficulty are responsible for differences in the pupil response to RAND-REG.

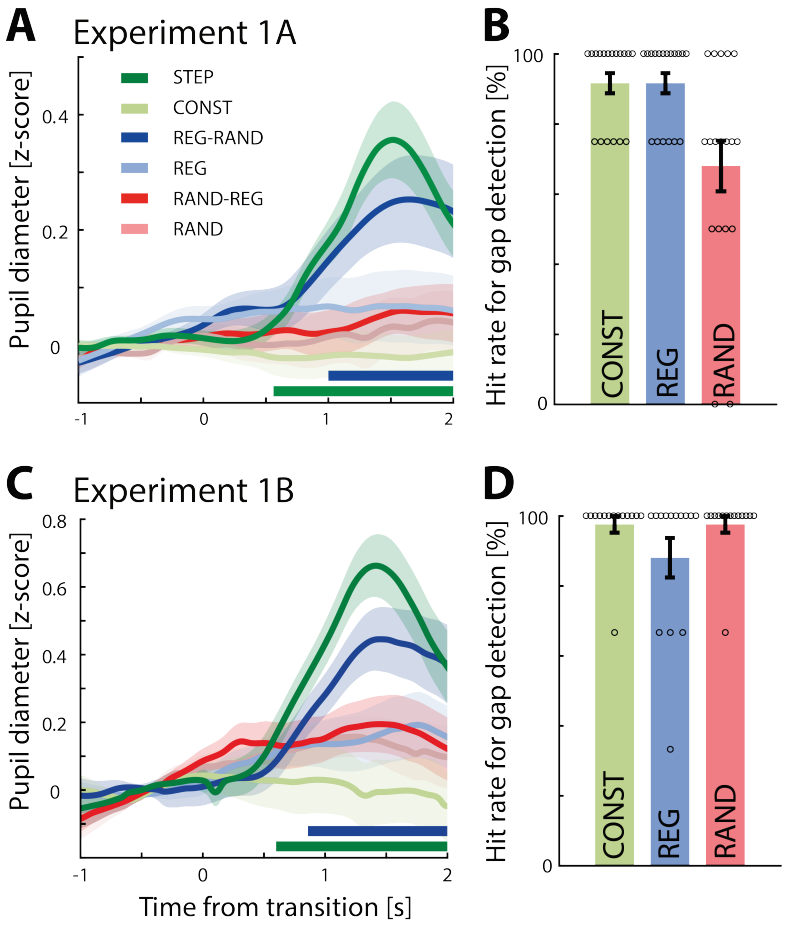


Figure 3.2 Pupil response and behavioural results of Experiment 1. [A and C] The solid line represents the average normalised pupil diameter as a function of time relative to the transition. The shaded area shows ± 1 SEM. Coloured horizontal lines at the bottom indicate time intervals where cluster-level statistics show significant differences between each change condition and its no-change control ($p<0.05$). [B and D] Behavioural results for the gap detection task. Black circles represent individual participant data. The error bars are ± 1 SEM.

3.3 Experiment 1B

3.3.1 Motivation

To ensure that differences in behavioural performance observed for Experiment 1A are not confounding pupil dilation responses to the pattern transitions, the previous paradigm was re-run whilst adjusting the gap duration to equate for task difficulty. Specifically, the gap duration was lengthened in the RAND condition from 100 to 150ms.

3.3.2 Methods

Participants

Data from 14 new participants (13 females; aged 22-26, average 23.1) were used in the analysis. Five additional participants were excluded due to high blinks rates. One additional participant was excluded due to poor behavioural performance (0% gap detection hit rate in REG sequences).

Stimuli and Procedure

The stimuli and procedure were identical to that of Experiment 1A, except that only three blocks, resulting in the presentation of a total 108 stimuli (18 of each condition shuffled and presented in random order), on the basis that previous data indicated that this was sufficient to observe the relevant effects.

Each of three blocks contained six gap-containing “target” sequences, comprising of one of each stimulus type; thus, each condition had 15 gap-free trials for further analysis. The gap was 50ms long (one missing tone) in CONST and STEP, 100ms long (two tones) in REG and REG-RAND, and 150ms long (three tones) in RAND and RAND-REG (Figure 3.3).

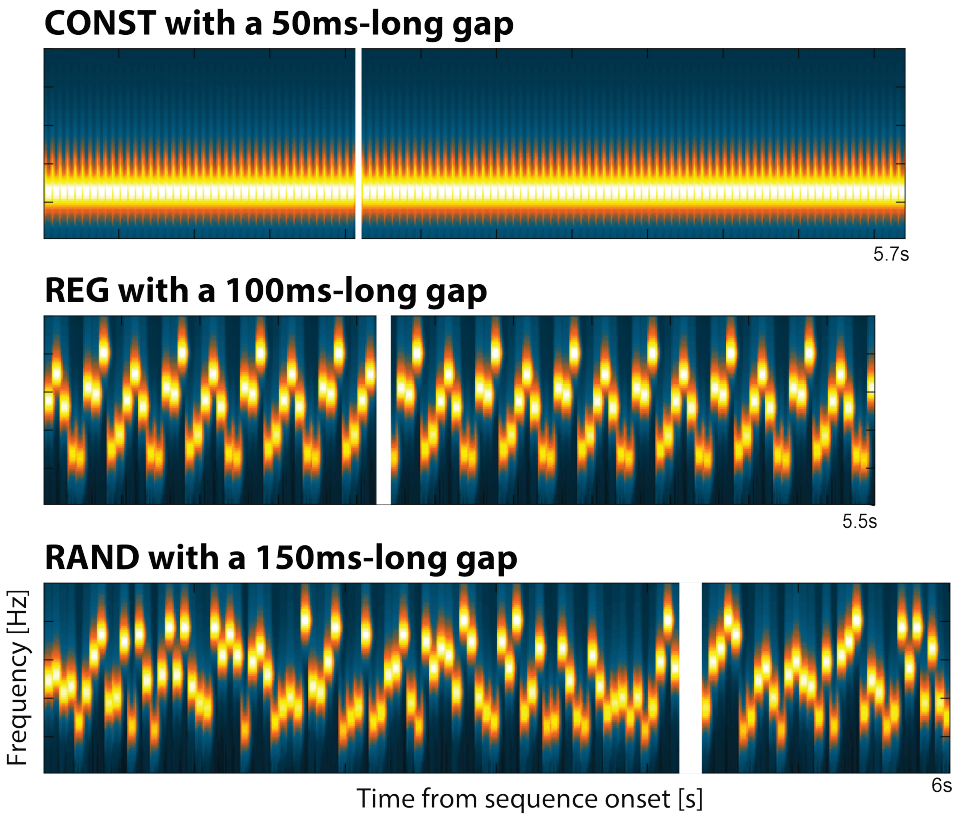


Figure 3.3 Example spectrograms of "gap" stimuli used in the gap detection task. The transition conditions are not shown here. The white vertical bar in the plot indicates the different length of gaps. [Top] CONST sequences (or either the pre- or post-transition portions of STEP sequences) might contain a 50ms-long gap (one missing tone) any time before the offset. [Middle] REG sequences or the REG portion of a sequence (the pre-transition part of REG-RAND, and the post-transition of RAND-REG) might contain a 100ms-long gap (two missing tones). [Bottom] From Experiment 1B, to equalise the gap detection performance across conditions, the gap in the RAND portion of sequences was extended to 150ms (three missing tones). At most, there are no more than one gap per trial. Whether and when the gap would happen in the sequence was randomly assigned for each trial.

3.3.3 Results

Behavioural results

A repeated measures ANOVA shows that the hit rates ($F(2,26)=2.167$, $p=0.135$) and false alarm rates ($F(2,26)=1.000$, $p=1.000$; no participants had false alarms in any conditions) for the gap detection task are not significantly different across conditions. The hit rate in RAND is significantly lower than CONST ($p=0.026$) and REG ($p=0.026$), while CONST and REG do not differ significantly ($p=1.000$; Bonferroni corrected).

As the behavioural results approach ceiling performance, an arcsine (square root) transformation was applied to the hit rates and the false alarm rates. Again, a repeated

measures ANOVA shows no significant effect of stimulus condition on the arcsine transformed hit rates ($F(2,26)=2.115$, $p=0.141$) and the arcsine transformed false alarm rates ($F(2,26)=1.000$, $p=1.000$). This suggests that the revised paradigm successfully eliminates performance differences between conditions (Figure 3.2D).

Average pupil diameter from stimulus transition

As seen in Figure 3.2C, the pupil dilation response pattern observed in Experiment 1A has been replicated by Experiment 1B. The divergence of STEP from its control CONST is significant from 600ms post-transition. Meanwhile, REG-RAND begins to significantly diverge from its control (REG) at 860ms, which is approximately the same time as in Experiment 1A. Again, there is no significant difference between RAND-REG and RAND throughout the epoch.

In a similar manner to that of Experiment 1A, the difference between REG-RAND and RAND-REG commences around 1020ms post-transition. A significant difference exists between STEP and REG-RAND from 740ms onwards – STEP elicits a larger response than REG-RAND; this was not observed in Experiment 1A.

Pupil event rates from stimulus transition

There is the potential that the null-effect of the pupil response to RAND-RED may be due to a large spread in timing (i.e. the events are not time locked) of the onset of pupil dilations, leading to a reduction in amplitude due to the limitations of across-trial averaging (see Chapter 2). To examine this possibility, a further examination of pupil dilation and pupil constriction rates was performed (see more detail about this analysis in Chapter 2). As described in Chapter 2, pupil dilation rate analysis focuses on the timing – specifically the onset – of the pupil dilation responses in a single trial level. The onsets of pupil dilations are presented in a temporal raster plot in the left panel of Figure 3.4. To demonstrate the stability of the thresholds – applied to reduce the noise caused by momentary amplitude flutters in the pupil data – the pupil dilation rate is presented with two threshold values, 75ms and 300ms (see Chapter 2 for a detailed explanation).

As pupil (dilation and constriction) events are relatively rare – typically one event every two seconds in the pre-transition interval (Chapter 2) – statistical analysis includes participants from both Experiment 1A and Experiment 1B (32 participants overall).

The incidence rate of pupil dilations can be estimated by dividing the data into temporal windows. Events are tallied in non-overlapping windows of 500ms to perform paired t-tests between transition conditions and their respective non-transition controls. The window length is deliberately large to allow the analysis to capture pupil dilations (if any) evoked by RAND-REG; as there is the distinct possibility that the increased pupil dilation rate may be obscured by a wide temporal spread, a large window would be required to ensure this is captured successfully. Moreover, as mentioned before, pupil dilation events are relatively rare, so a wide window would ensure sufficient events in each window for statistical analysis.

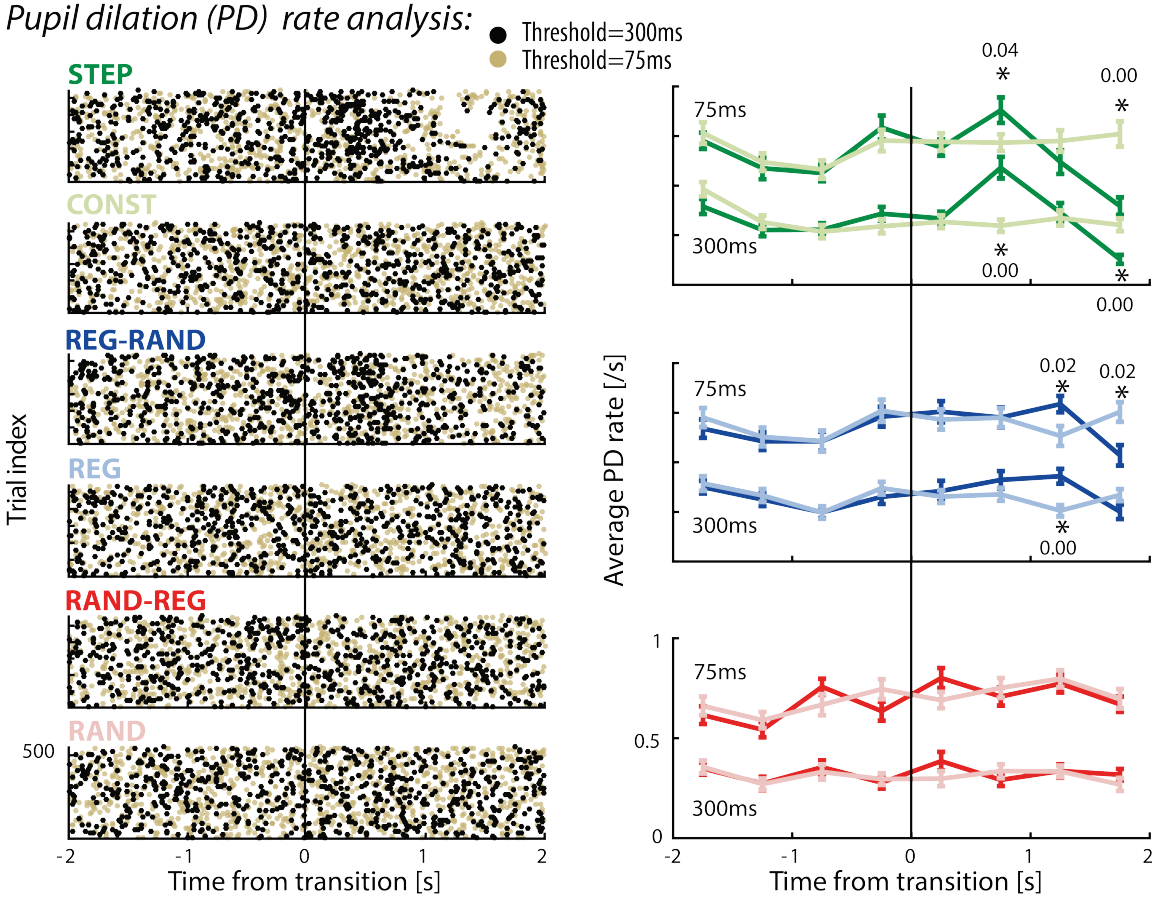
Figure 3.4 (top left panel) shows the raster plot of pupil dilation onsets from all trials of all participants (32 participants from Experiment 1A and Experiment 1B), over an interval of two seconds either side of the transition. These provide an intuitive view of the fluctuating nature of pupil responses: the pupil dilates and occasionally constricts over time. As evidenced by the no-change conditions (CONST, REG and RAND), occurrences of pupil dilation events appear to be uniformly distributed over time. In other words, the pupil dilates at a consistent rate in the absence of any pattern changes. However, for STEP and REG-RAND, the distribution of pupil dilation events become much denser after the transition – indicating an increase in pupil dilation rate. This high-density interval is centred around 500ms post-transition, with a width of under 500ms. Interestingly, immediately following this high-density period, pupil dilation events become much sparser and almost absent for around 500ms, which is particularly apparent in the STEP condition. This ‘increase-then-decrease’ pattern of pupil dilation events is much more evident once the rate changes are estimated by tallying the events using non-overlapping 500ms windows. As shown in the right-hand panel, STEP and REG-RAND demonstrates a significant increase in rate shortly after the transition, followed by a dramatic decrease which reaches significance just before the sequence offset. Interestingly,

the significance of the later decrease seems to be even stronger than that of the early increase. This interval of pupil dilation absence might reflect the refractory period after the onset of time-locked evoked pupil dilation events; a dilated pupil can dilate no more. The finding that the pupil dilation rate increases after transitions in the STEP and REG-RAND sequences is stable and robust in the results from thresholds of 75ms and 300ms. However, RAND-REG exhibits no such change at all; comparing results across the two thresholds demonstrates the stability of this effect. This result pattern remains even when the comparison is conducted between the transition condition and the control with physically identical post-transition part; when comparing REG-RAND with RAND, REG-RAND has significantly higher pupil dilation event rate after transition, whilst comparing RAND-REG with REG, RAND-REG still does not show any significant change in its pupil dilation event rate.

In a similar manner, the pupil constriction (PC) rate is presented in the bottom panel of Figure 3.4. Likewise, for the no-change conditions, the pupil constriction rate is generally consistent throughout the epoch. For STEP, the pupil constriction rate shows a decrease shortly after the transition, followed by a rather conspicuous increase, which mirrors the 'increase-then-decrease' pattern of the pupil dilation rate. A similar, but not significant, trend can be observed in the pupil constriction rate for REG-RAND. Combined with the time course of the pupil dilation rate (Figure 3.4, top panel), the event rate analysis of STEP and REG-RAND show that the evoked pupil dilations are time-locked with a moderate jitter (on the order of a few hundred milliseconds) after the transition. The time-lock effect is apparent for pupil dilation events through the 1st second post-transition, and pupil constriction events through the 2nd second. Nevertheless, in parallel with the pupil dilation rate analysis, no change can be observed in the pupil constriction rate for RAND-REG, further confirming the null effect in pupil responses for this transition. Finally, the results from both thresholds 75ms and 300ms remain similar in the pupil constriction rate analysis, suggesting that these two thresholds are applicable for both types of pupil events.

These results are generally consistent with findings from across-trial averaging analysis of the pupil diameter: the dynamics of pupil responses show a robust change post-transition in both STEP and REG-RAND. However, no responses were observed for RAND-REG – no matter the subject of analysis, be it absolute pupil diameter, pupil dilation rate or pupil constriction rate. Secondly, the null effect of average pupil diameter in RAND-REG cannot be explained by the temporal spread of pupil dilation events, because no difference exists between RAND-REG and its control RAND, and there is no evidence for any time-locked evoked pupil dilations even when using a wide non-overlapping window. Thirdly, in STEP, both pupil dilations and pupil constrictions have a relatively small temporal spread after the transition. Like STEP, REG-RAND also evokes pupil dilations shortly after the transition, although the centre of the temporal distribution seems to be slightly later than STEP (by one time window, approximately 500ms). Fourth, the pupil dilation and pupil constriction rates show mirrored dynamics: the pupil dilation rate exhibits a dramatic 'increase-then-decrease', while the pupil constriction rate shows a reversed pattern. A refractory period is apparent following the cluster of pupil dilations onsets for STEP sequences from 1 to 1.5s after transition (Figure 3.4, top left). Notably, the timing of the increase in the pupil constriction rate (after 1.5s post-transition) comes later than the decrease in the pupil dilation rate (after 1s post-transition). Finally, it is noticeable when comparing the two metrics that the pupil dilation rate might be more robust for statistical analysis and more consistent with the standard across-trial averaging pupil diameter result. Due to this observation, the following chapters will focus on pupil dilation rate analysis, if applicable.

Pupil dilation (PD) rate analysis:



Pupil constriction (PC) rate analysis:

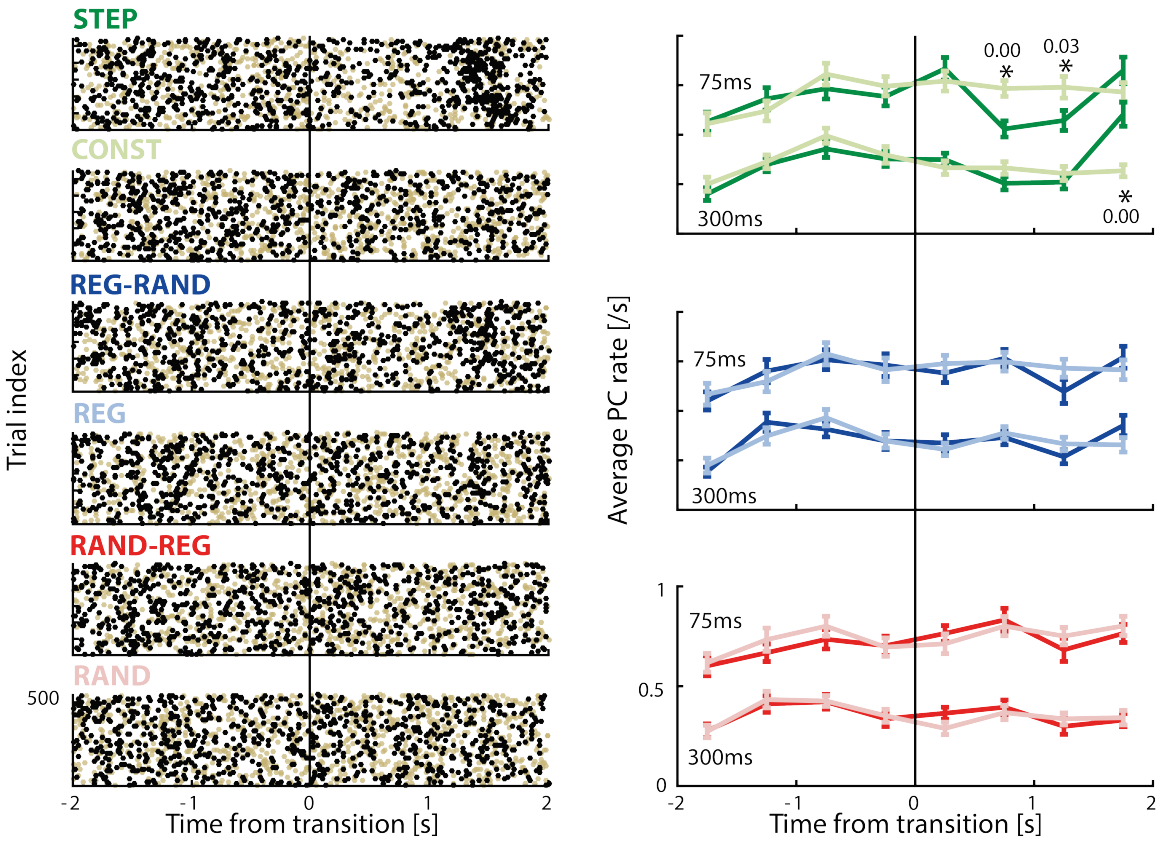


Figure 3.4 Pupil dilation and pupil constriction rate results for Experiment 1. [Top left] Raster plots of pupil dilation (PD) events extracted from all trials and all participants. Each black dot represents the onset of a pupil dilation with a duration of at least 300ms, while yellow coloured dots represent pupil dilation onsets with a shorter threshold duration of 75ms. The transition time is indicated by a black vertical line. [Top right] Average pupil dilation onset rate as a function of time relative to the transition: Top: STEP and CONST; Middle: REG-RAND and REG; Bottom: RAND-REG and RAND. Intervals containing significantly different onset rates are labelled with an asterisk along with their p values. [Bottom] The lower panels present the pupil constriction (PC) rate results in the same manner as those of the top.

Average pupil diameter and pupil event rates from stimulus onset

No indication of pupil responses after the RAND-REG transition have been observed in the average pupil diameter result (Figure 3.2) in both Experiments 1A and 1B, which is consistent with the pupil event analysis shown above (Figure 3.4). One might suspect that this null-effect in RAND-REG might be partially caused by differences in the pre-transition period. To examine this possibility, both analyses – average pupil diameter and pupil event rates – were conducted over the pre-transition periods (Figure 3.5).

Indeed, there is some evidence that the pupil dilates more for RAND. As plotted in the pupil event rate analysis (Figure 3.5A), a series of repeated measures ANOVA run at four intervals pre-transition show a significant increase in the pupil *dilation* rate over the 1-to-0.5s interval before the RAND-REG transition ($p=0.002$, Figure 3.5A top). Nevertheless, no difference in pupil *constriction* rates can be observed across conditions before transition (Figure 3.5A bottom).

Figure 3.5B presents the average pupil diameter from sequence onset. Before transition, no significant differences are observed between RAND and REG in both Experiments 1A and 1B. Interestingly, Experiment 1A exhibits a divergence between RAND and CONST from 1960ms post-onset (Figure 3.5B left), which may be an artefact induced by the unbalanced task difficulties of the experiment.

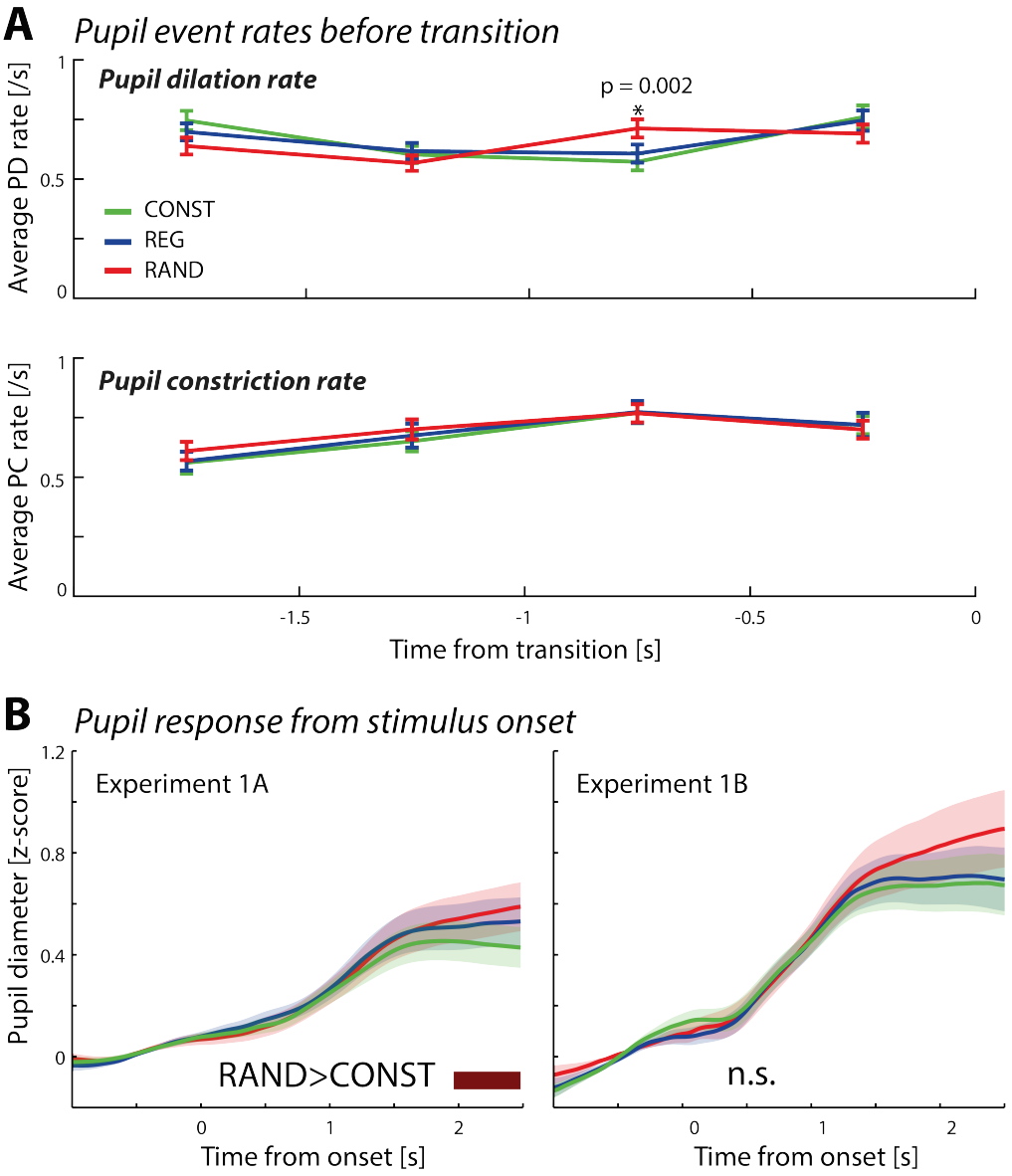


Figure 3.5 Pre-transition pupil responses for Experiment 1. [A] Average pupil dilation (PD) onset rate and pupil constriction (PC) onset rate as a function of time relative to the transition (with a 75ms threshold), pooling all participants from both Experiments 1A and 1B, and collapsing all three pre-transition conditions: CONST with STEP, REG with REG-RAND, and RAND with RAND-REG. Asterisks, along with p values, denote intervals where the rates are significantly different ($p<0.05$). As the two thresholds of 75ms and 300ms display the same effects, the data for the latter threshold are not shown here. [B] Average pupil diameter over time relative to the onset of Experiment 1A and Experiment 1B. The shaded area around the solid lines shows ± 1 SEM. Cluster-level statistics show a significantly different ($p<0.05$) between RAND and CONST in Experiment 1A over the time interval indicated by the solid line at the bottom of the graph.

3.4 Discussion

Experiments 1A and 1B both employ rapid auditory sequences featuring transitions between regular and predictable, or random and unpredictable structures. Previous work (Barascud et al., 2016) has demonstrated remarkable behavioural and brain response sensitivities to these pattern changes, consistent with precision based predictive coding accounts of perceptual inference.

At 50ms (20 Hz) the tone durations are comparable to the rates of many environmental sounds; this is still below the ranges for notes in musical melodies and thus remains too rapid to enable any form of explicit reasoning regarding the sequence structure. Instead, the emergence or violation of regularity appears to perceptually 'pop out' from the ongoing sequence irrespective of participative effort. This is hypothesised (see Barascud et al., 2016) to be supported by a mechanism which automatically maintains and updates a statistical model of the auditory input, searching for violations of this structure which could be indicative of relevant changes in the environment.

In these two experiments, naïve participants listen to the sounds but do not make any decisions related to the transitions contained within. To ensure active listening to the tone-pip sequences, participants were instructed to look for a rare short gap imbedded in the sequences, and importantly, the gaps were not associated with the transitions and were equally easy to detect in any given condition. Any trials containing gaps or responses – irrespective of the accuracy of the response – were excluded from analysis. Using this task, transition-related pupil responses were measured in the absence of behavioural decision-making at the time when the change was happening, demonstrating a robust pupil dilation response evoked by a violation of acoustic patterns in rapid sound sequences. The pupil dilations evoked by auditory transitions in STEP and REG-RAND started around 0.5s after the transition and peaked 1s later. However, so far, we have not observed any pupil responses associated with the emergence of regularity (RAND-REG).

This set of results confirms predictions. The abrupt pattern changes in rapid complex sound sequences can indeed evoke transient pupil dilations, suggesting that the NE system is sensitive to rapidly changing acoustic signals. Importantly, these responses only existed for the STEP and REG-RAND transitions, because only these conditions were associated with an unexpected uncertainty, signalled by a phasic NE response and observed as transient pupil dilation. Meanwhile, the RAND-REG transition did not evoke transient pupil dilation because it represents an increase in precision (a reduction of expected uncertainty) which is not associated with the phasic NE response and thus elicits no transient pupil dilation.

3.4.1 The pupil dilation response is sensitive to the violation of sequence regularity.

Many studies demonstrate that salient (Friedman et al., 1973; Liao et al., 2016a, 2016b; Steinhauer and Zubin, 1982; Wang et al., 2014) or surprising (Nassar et al., 2012; Preuschoff et al., 2011; Sara and Bouret, 2012) signals evoke pupil responses. This has been proposed to reflect the LC's involvement in supporting behavioural adaptation to unexpected environmental changes. This experiment demonstrates that pupil responses can be evoked by rapid sound sequences with complex pattern violations – not just simple novelties. The prediction error associated with the first violating tone likely triggers the pupil-linked LC-NE system, as implied by the resetting hypothesis (Dayan and Yu, 2006). Together with evidence from MEG responses (Figure 1.6); this is associated with a mismatch negativity-like response (Näätänen et al., 2007) followed by a distinct rapid decrease in the amplitude of the sequence evoked sustained response (Barascud et al., 2016), indicative of a rapid reorganization of the underlying network and a transition to a different brain state.

The onset of the pupil dilation response (the time at which the transition condition begins to diverge from its no-change control) is at around 500ms post-transition; the basic latency of the pupil reflex (rapid response to light stimulation) is commonly estimated to be around 200ms (Feinberg and Podolak, 1965), suggesting that the REG-RAND transition-related signal reached the pupil no later than about 500ms post-transition. This latency is within

the same time range as MEG responses recorded from the auditory cortex (Figure 1.6; Barascud et al., 2016) demonstrating very rapid signalling from the auditory system to the LC.

Overall, this result means that NE's role in signalling unexpected uncertainty extends to rapid timescales and, critically, highlights the fact that this role is not limited to decision making – a primary focus of many previous studies – but might play a more fundamental critical role in perception.

3.4.2 The pupil dilation response does not respond to the emergence of patterns.

In contrast, no pupil responses were observed to the *emergence* of regularity. The disparity in the pupil responses between REG-RAND and RAND-REG is particularly interesting because these two transitions were both behaviorally detectable (Barascud et al., 2016). In a later chapter (Chapter 6), this will be demonstrated in a behavioural experiment where the participant is be instructed to actively detect and report the transitions – all three transitions are well-detected by active listeners, with a 100% hit rate and approximately 0% false positive rate. Previous MEG results (Barascud et al., 2016) also show that distracted passive listeners could detect the transitions REG-RAND and RAND-REG equally well.

Moreover, the null-effect in RAND-REG cannot be explained by excessively slow detection, because all three transitions can be detected very rapidly in under one second, as shown by Barascud et al. (2016). Although the reaction time to RAND-REG is slightly slower than REG-RAND by about 0.2s (Chapter 6, also see Barascud et al., 2016), even with this in consideration, detection of the transition RAND-REG should occur substantially before sequence offset. The latency differences in the brain responses for both transitions have been found to be also very small, under 100ms (Figure 1.6, Barascud et al., 2016).

Similarly, the spread of change detection times to RAND-REG should not the cause for the null-effect in RAND-REG either. This again will be further investigated in Chapter 6 where behaviour will be introduced, producing results that show that the reaction time distribution of

RAND-REG is no wider than that of REG-RAND, in fact, the converse is true: RAND-REG's spread is even smaller than REG-RAND.

Even taking the latency of pupil responses into account, with typical latencies of around 0.5 seconds for event-evoked pupil dilations, the epoch (encompassing two seconds post-transition) should be sufficient for the emergence of pupil responses. If the transition RAND-REG does indeed evoke a pupil response, it should be observable given this relatively long epoch.

Furthermore, to rule out the possible confound of cognitive processing load on the pupil size, the adjusted tasks in Experiment 1B ensure equal performance across conditions, thus eliminating task differences due to difficulty and its consequent effect on performance. Another important aspect is that the null effect in average pupil diameter is not due to averaging across trials because of there no apparent increase in pupil dilation rate to the change.

Another possible explanation for this null effect is saturation to RAND: while listening to the RAND portion of RAND-REG, the pupil has steadily dilated and reached saturation at its maximum. However, pre-transition pupil response analysis partially rules this out. Despite this, the most conclusive test of the saturation hypothesis is to demonstrate that certain transitions from RAND do evoke a pupil dilation response. This will be investigated in Chapter 5.

4 Is the pupil dilation response predominantly a result of novelty or pattern violation per se?

4.1 Motivation

Experiment 1 established that the pupil dilates to STEP and REG-RAND but not RAND-REG, suggesting a sensitivity that favours violation, but not the emergence, of complex regularity patterns.

As mentioned before, the first post-transition tone of REG-RAND can be controlled to ensure immediate violation of the outgoing REG pattern. However, Experiment 1 did not include this restriction. As REG is constructed from a subset of ten frequencies from the pool whilst RAND spans all 20, the REG-RAND transition could feature a deviant frequency. On this subject, Liao et al. (2016b) observed pupil dilations to deviant sounds in repetitive sound sequences, finding that the pupil dilation reflects the degree of deviance, with greater deviances eliciting larger pupil dilations.

As previous experiments did not explicitly control deviants during stimulus generation, it is likely that a significant number of pupil dilations responses in REG-RAND are merely evoked by a novel frequency, and not intrinsic statistical changes in the complex sequence pattern. This novelty may be central to explaining pupil dilation response patterns in Experiment 1: Both STEP and REG-RAND evoked pupil dilation responses because both transitions feature a deviant frequency; meanwhile, RAND-REG manifests as a reduction in

alphabet size, thus no deviant and no pupil dilation response. Henceforth, to understand whether pupil dilation responses are predominantly elicited by novelty or the violation of regularity, the stimulus set in this Experiment 2 (Figure 4.1) encompasses a combination of conditions where the transition is expressed as a pattern change with or without a deviant frequency.

4.2 Experiment 2

4.2.1 Methods

Participants

Data from 18 new participants (15 females; aged 20-35, average 25.1) are reported. Two additional participants were excluded: one due to high blink rates, and one due to wandering gaze.

Stimuli and Procedure

The stimulus set is shown in Figure 4.1. This experiment features several new sequences: *REG10* sequences were generated by randomly selecting ten frequencies from the pool and then iterating that sequence to create a regularly repeating pattern, with this process repeated per trial. *RAND10* sequences were generated by randomly selecting ten frequencies from the pool and then presenting them in random order, with a single constraint to ensure no consecutive repetitions. *REG10-RAND10* and *RAND10-REG10* sequences were created by concatenating REG10 and RAND10 sequences using the same subset of 10 frequencies (with subsets randomised every trial). In this way, the transition was solely manifested as a pattern change without the occurrence of a deviant frequency.

To examine responses to transitions involving frequency deviants, two further new transition conditions – *REG10-RAND10d* and *RAND10-REG10d* (where 'd' stands for 'deviant') – used subsets of frequencies selected to ensure no overlap: the transition was thus manifested as both a change in pattern but also the frequency content of the sequence. The

stimulus set also included *REG10-RAND20*, *RAND20-REG10* and *RAND20* sequences, with the RAND20 portions constructed by sampling frequencies from the entire pool of 20.

As mentioned before, to avoid possible confounds due to different probabilities of stimulus representation, trials with and without a change should be presented in equal numbers. This experiment contained three types of REG-RAND transitions (REG10-RAND10, REG10-RAND10d and REG10-RAND20) and three types of RAND-REG transitions (RAND10-REG10, RAND10-REG10d, RAND20-REG10), however, noteworthily, the RAND-REG transition could start with a RAND10 sequence or a RAND20 sequence. Thus, in the present experiment, the controls were REG10 (for all three REG-RAND-type transitions), RAND10 (RAND10-REG10 and RAND10-REG10d) and RAND20 (RAND20-REG10). This resulted in an uneven, but equally balanced and represented, number of control trials; the REG10 control appears three times more frequently as there are three types of REG-RAND transitions, likewise the RAND10 control appears twice as frequently.

In total, the experiment contained 240 stimuli: 60 REG10, 20 REG10-RAND10, 20 REG10-RAND10d, 20 REG10-RAND20, 40 RAND10, 20 RAND10-REG10, 20 RAND10-REG10d, 20 RAND20 and 20 RAND20-REG10. 20% of the sequences contained a gap, with equal probability spread across conditions. Gap lengths were as in Experiment 1B: 100ms long (two tones) in REG and REG-RAND-type conditions, and 150ms long (three tones) in RAND and RAND-REG-type conditions. These stimuli were presented in random order and consecutively in five blocks.

The stimulus length was randomly varied between 120 and 160 tones (6–8 seconds), with the transition jittered between 60 and 80 tones after sequence onset. On visual inspection of the pupil diameter result in the previous experiment (Figure 3.1), it was apparent that the whole form of the curves was not captured within the epoch. Thus, from this experiment onwards, the post-transition lengths are extended by one second, resulting in a post-transition epoch of three seconds.

Moreover, when compared to previous experiments, this experiment presented many more (and longer) stimuli, so participants were asked to rest longer between blocks to reduce fatigue. In order to efficiently use the experimental facilities, two participants were alternated between blocks: one rested while the other completed the block. Therefore, participants typically had over 10 minutes rest between blocks, extending the overall experimental session to just below three hours.

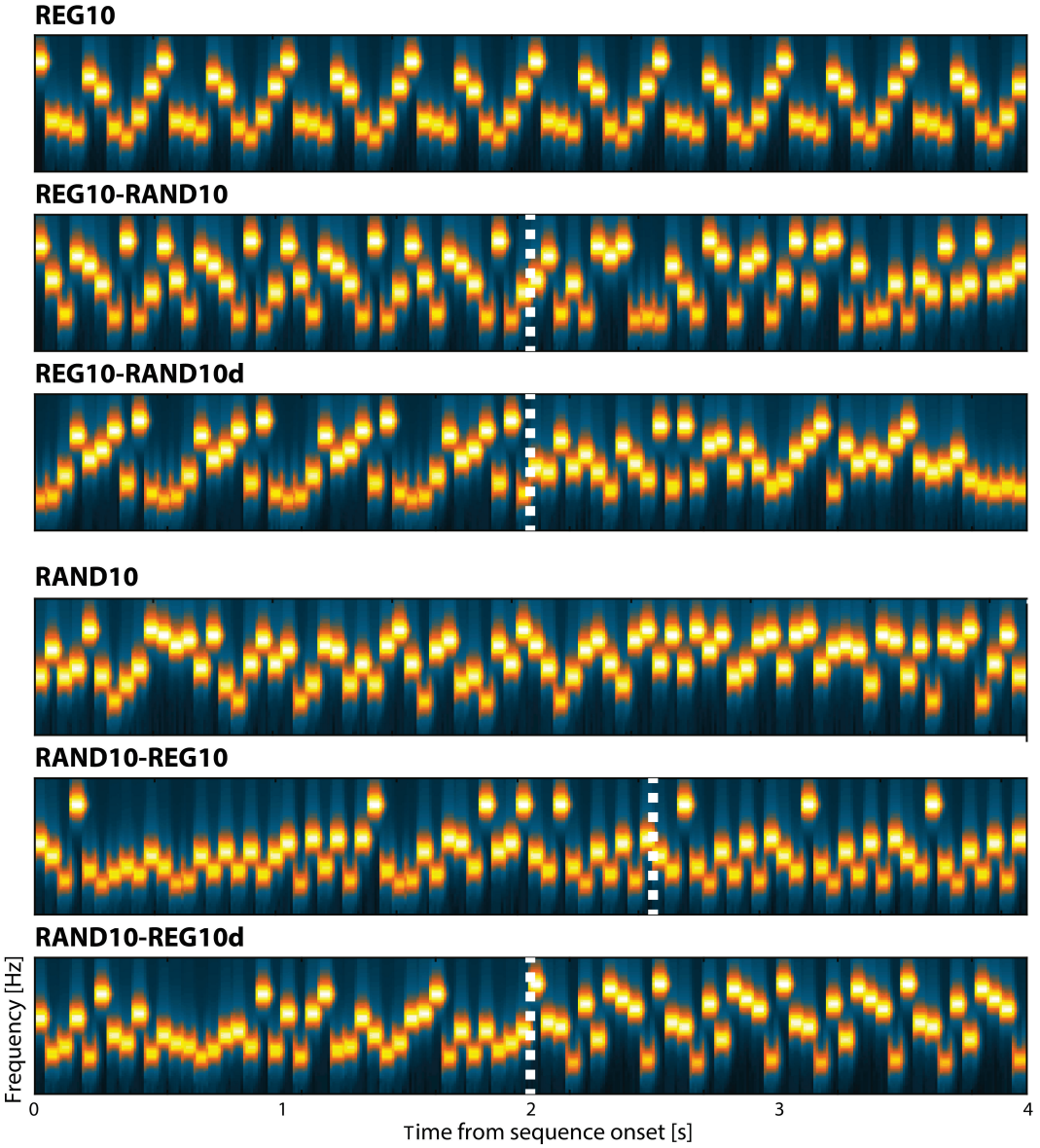


Figure 4.1 Example spectrograms of the stimuli used in Experiment 2. [Top three] REG RAND type conditions: REG10, REG10-RAND10, and REG10-RAND10d. REG10-RAND10 sequences consist of a fixed set of ten frequencies (drawn anew for each trial). In REG10-RAND10d sequences, the frequency subset changes at the transition such that the REG and RAND portions of the sequence are constructed from different (non-overlapping) frequencies. [Bottom three] RAND-REG-type conditions: RAND10, RAND10-REG10, and RAND10-REG10d. In a similar manner, a fixed subset of ten frequencies features throughout each trial in RAND10-REG10. RAND10-REG10d consists of different frequency sets for the REG and RAND portions of the sequence. The stimulus set also contained RAND20 (identical to RAND in Figure 3.1), RAND20-REG10 ('RAND-REG' in Figure 3.1) and REG10-RAND20 (REG-RAND in Figure 3.1).

4.2.2 Results

Average pupil diameter from stimulus transition

The results of Experiment 2 are shown in Figure 4.2. The pupil responses to REG10-RAND20, RAND20-REG10 and their respective controls REG10 and RAND20 (Figure 4.2A) replicate the pattern observed in Experiment 1: REG10-RAND20 diverges from REG10 at 780ms post-transition while RAND20-REG10 does not differ statistically from RAND20.

Figure 4.2B plots all conditions containing a transition from a regular to a random pattern. These conditions evoke a marked pupil dilation response relative to the REG10 control. The pupil dilation response to REG10-RAND10 starts to increase from 420ms and becomes statistically significant from REG10 860ms post-transition, before reaching a peak at around 1620ms. Meanwhile, the response to REG10-RAND10d starts at 400ms significantly diverges from REG10 at 800ms, peaks at 1380ms.

In contrast, no significant differences were observed for any of the random-to-regular transitions (Figure 4.2C). Surprisingly, this was also the case for the RAND10-REG10d condition where the RAND and REG sequences featured different frequency content and patterns. While a small peak is visible after the transition, is not significantly different from RAND20 or RAND10.

Figure 4.2D shows the pupil response from stimulus onset. As in Experiment 1 (Figure 3.1B), the pupil diameter for all conditions gradually increased from the sequence onset. Moreover, this experiment (Figure 4.2B) exhibits no apparent difference between REG, RAND10 or RAND20 before the transition.

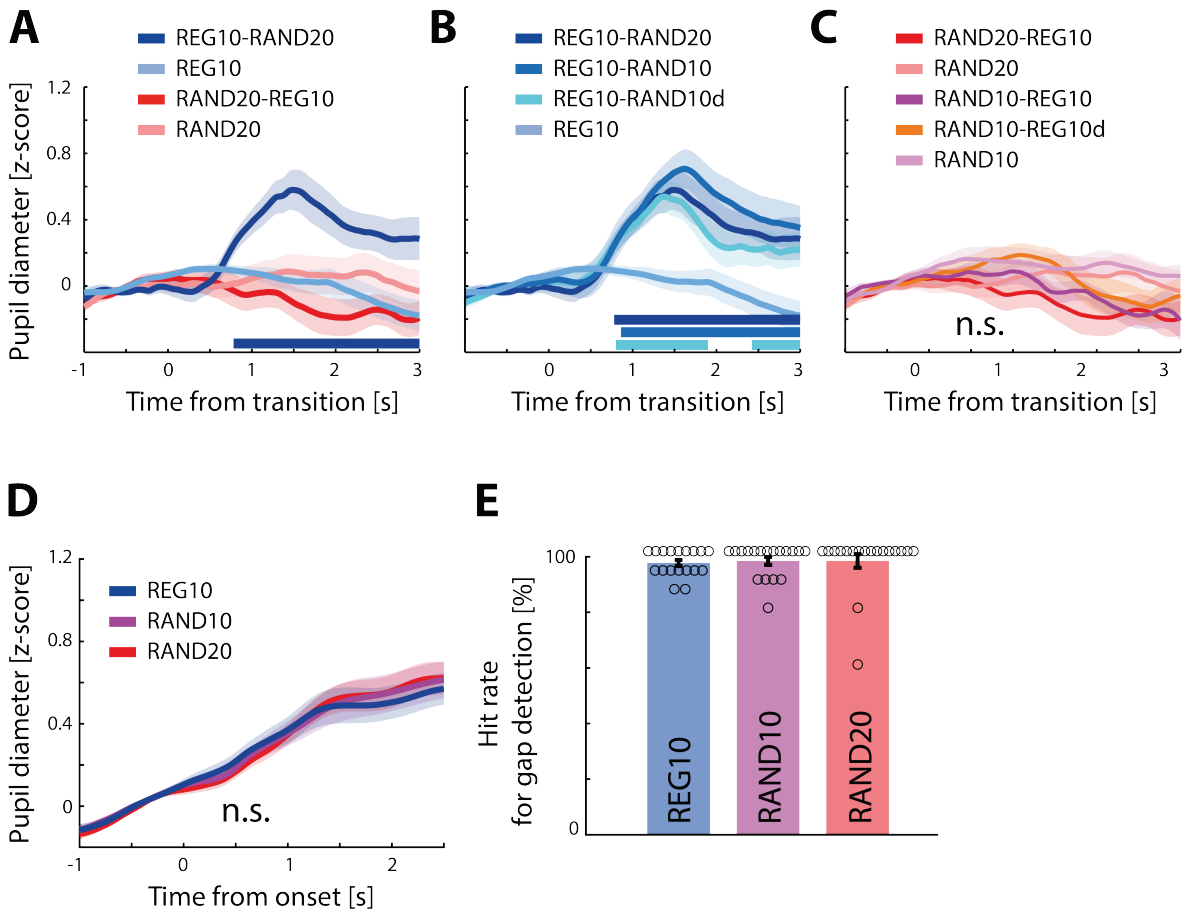


Figure 4.2 Pupil response and behavioural results of Experiment 2. [Top panels: A, B, C] Average pupil diameter over time relative to the transition. The shaded area around the solid lines shows ±1 SEM. Time intervals where cluster-level statistics show significant differences between each transition condition and its non-transition control ($p<0.05$) are indicated with identically-coloured horizontal lines below the plots. For clarity, the pupil dilation responses are plotted in three groups: [A] The stimuli also used in Experiment 1: REG10-RAND20, RAND20-REG10 and their corresponding controls. [B] All stimuli containing transitions from REG10. [C] All stimuli containing transitions from RAND10. [D] Average pupil diameter over time from onset. [E] Behavioural results for the gap detection task with 1 SEM error bars and black circles representing individual participant data.

Behavioural results

The similar hit rates of the gap detection task in REG10, RAND10 and RAND20 confirms the equal task performance across conditions in this experiment (Figure 4.2E). A repeated measures ANOVA shows no effect of condition on the hit rates ($F(1.519,25.816)=0.057$, $p=0.902$, with Greenhouse-Geiser correction as Mauchy's Test of Sphericity indicates a violation of the assumption of sphericity) or false positive rates ($F(2,28)=1.000$, $p=0.381$). As performance approaches the ceiling, the hit rates and false alarm

rates were arcsine transformed before applying a repeated measures ANOVA on the resulting it rates ($F(1.427,24.259)=0.028$, $p=0.934$, Greenhouse-Geisser corrected) and false alarm rates ($F(1.397,23.752)=0.933$, $p=0.376$, Greenhouse-Geisser corrected); both show no effect of condition on task performance.

4.3 Discussion

In summary, the experiment of this chapter replicates the disparity in pupil responses to violations (REG-RAND), and emergences of regularity (RAND-REG) observed in Chapter 1. Importantly, this persists even when controlling the frequency subsets of the patterns before and after transition (i.e. the set of tone frequencies used to compose the sequence). There are two main findings:

First, the pupil dilation response observed in Chapter 1 to violations of regularity cannot be attributed merely to deviant detection. By ensuring that the subset of tone frequencies remains identical before and after the transition, the same tones appear throughout the entire sequence, thus creating a deviant-free transition consisting purely of regularity violation – this is the REG10-RAND10 transition. Pupil responses remain robust to this pure pattern violation, further confirming the finding that the LC-NE system is sensitive to complex pattern violations and not merely just novelty detection.

The second finding concerns the lack of pupil responses to any random-to-regular transition (RAND-REG), even when the physical features of the REG sequences are completely distinct from the RAND sequence preceding it – for instance when using a different set of frequencies. This further demonstrates the robustness of the null effect of pupil responses to RAND-REG transitions. Considering the well-established pupil response to deviant detection (Friedman et al., 1973; Liao et al., 2016b; Nieuwenhuis et al., 2011; Qiyuan et al., 1985; Raisig et al., 2010; Wetzel et al., 2016), it is also surprising that the combination of completely novel frequencies with the emergence of regularity do not evoke pupil dilation

responses either. One possibility for this null-effect of deviant frequencies is an insufficient difference between the new frequencies in REG and the outgoing frequencies in RAND. Previously, Liao et al. (2016b) found that while white noise oddballs evoke strong pupil dilation responses in passive listeners, frequency deviants did not evoke pupil dilation responses. Wetzel et al. (2016) also found that the size of a pupil dilation response might depend on the magnitude of the difference between the intrinsic properties of the deviants and standard signals; if this is the case, it would be interesting to explore how large this difference needs to be to stably evoke pupil dilations. Another possibility is related to the presentation rate of the tone sequences, as previous studies utilise much slower presentation rates (cf. (Liao et al., 2016b) presenting at 2.86Hz (50ms tones separated by 300ms), with the current study presenting at 20Hz (50ms tones with no gaps in-between)). With this in consideration, it is possible that deviant-evoked pupil dilations can only be observed at slower sound presentation rates, a possibility supported by the relatively slow evolution of pupil responses.

Of course, these effects could be the result of a convolution of the two reasons – insufficiently small differences and overly rapid presentation rate – amongst others. However interesting these questions, the pupillary data of these experiments cannot reveal any further evidence for either, and thus these questions would require further investigations with a specific focus on the relationship between pupil responses and deviant detection.

The null-effect of the pupil responses in the transition from random to regular patterns (RAND-REG) will be further investigated in the subsequent chapter. As mentioned in the discussion of Experiment 1, the pupillary saturation to RAND could explain this null effect; the possibility is highlighted by the absence of pupil responses to the transition in RAND10-REG10d of this experiment. Not only does RAND10-REG10d feature the emergence of a regular pattern, but also a completely new set of frequencies. Inconsistencies with prior observations of novelty-evoked pupil dilations (Liao et al., 2016b) may be because the frequency differences in the complex patterns of the present study are insufficient to evoke pupil dilations, but pupillary saturation over the course of the RAND portion is also a compelling

possibility; as such this saturation hypothesis is further investigated in the experiments of the following chapter.

5 The violation of randomness

5.1 Motivation

While the previous experiments show clear pupil dilation responses to the violation of regularity (REG-RAND), observations have not identified any apparent responses for the emergence of regularity (RAND-REG) even in the presence of deviant tones; it can be argued that this null-effect in the RAND-REG transition may not be due to insensitivity to regularities per se, but simply a result of saturated pupil diameter whilst listening to the pre-transition RAND portion of the stimulus. The most conclusive test of the saturation hypothesis should demonstrate that certain transitions from RAND do indeed evoke a pupil dilation response; this is the aim of the two experiments featured in this chapter.

As a natural extension of the present stimulus set, one suitable candidate likely to evoke a pupil dilation response is a transition from a random sequence to a single repeating tone (i.e. RAND-REG1). This transition should result in a strong pattern violation because the complex RAND portion of the sequence can be described by a rule whereby any tone can be followed by any other tone, but repetitions, especially more than once, are extremely rare. Indeed, the RAND20 sequences used in the present study have a 5% probability of 2-tone repetition and 0.25% for a 3-tone repetition (the probability is given by $p = 0.05^{n-1}$ for an n-tone repetition). Thus, the repetition of successive tones in the REG portion would strongly violate this 'rule' conveyed by the preceding random signal.

Indeed, previous MMN works have shown that occasional repetitions embedded in random sequences evoke an MMN-like response in distracted listeners (Horváth et al., 2001, 2007; Näätänen and Rinne, 2002; Wolff and Schröger, 2001), which in turn demonstrates that this rule – 'the same tone appearing two or more times consecutively is rare' – could be learned implicitly. Thus, since previous experiments in this thesis have demonstrated the capability of the pupil-linked LC-NE system to respond to a rapid strong pattern violation, it is not unreasonable to hypothesise that this new transition, RAND20-REG1, should also be captured by the LC-NE system and evoke phasic NE activity indexed as pupil dilation.

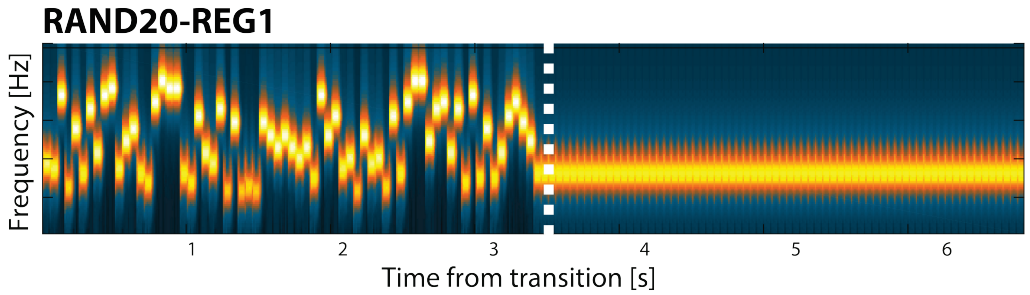


Figure 5.1 Example spectrogram of the stimulus RAND20-REG1. This new transition introduced in Experiment 3 is a transition from a random sequence composed of tones randomly drawn from a pool of 20 frequencies to a repeating sequence of a single tone randomly drawn from the pool. The selection of the single repeating frequency was random and chosen anew for each trial.

5.2 Experiment 3

5.2.1 Methods

Participants

Data from 12 new participants (9 females; aged 21 - 26, average 23.6) are presented.

Stimuli and Procedure

The stimulus set incorporated those from Experiment 1 and additionally a new stimulus – RAND20-REG1 – which consisted of a transition from a random sequence to a repeating single frequency tone (REG1) (see Figure 5.1 for a representative spectrogram).

Thus, this experiment contained seven conditions, STEP, CONST, REG10-RAND20, REG10, RAND20-REG10, RAND20-REG1, and RAND20. Additionally, since varying stimili probabilities can affect pupil responses (see Chapter 1), the trial count of the stimuli were adjusted to ensure balanced presentation probabilities: RAND20 is the control for both RAND20-REG10 and RAND20-REG1, so appearances of RAND20 should equal the total of both RAND20-REG10 and RAND20-REG1; the probability that a sequence starts with REG10 or CONST should be identical to RAND20, thus the total number of trials for the pair REG10-RAND20 and its control REG10 and the pair STEP and its control CONST should equal the sum of RAND20-REG1, RAND20-REG10 and RAND20.

The resulting stimuli numbers were 16 RAND-REG1, 16 RAND-REG10, 32 RAND, 32 REG, 32 REG-RAND, 32 CONT and 32 STEP, for a total of 288 trials, with one-third of the sequences containing a gap with lengths as in Experiment 1B. All were presented in random order across eight blocks. Since each block should have one gap trial per condition, and combined with the increase in the number of conditions and blocks in this experiment, the resulting proportion of gap trials was hence higher than in the previous experiments. As in Experiment 2, to avoid fatigue due to the excessive experimental length, two participants were alternated between blocks and thus received at least eight minutes of rest between blocks, resulting in an overall experimental length of around three hours.

5.2.2 Results

Average pupil diameter from stimulus transition

As seen in Figure 5.2A, the pupil response patterns observed in Experiments 1 and 2 have been replicated in the present experiment. The divergence of STEP from its control CONST begins to gain significance from 600ms post-transition. REG-RAND significantly diverges from its control (REG) from 860ms onwards, approximately the same time as in Experiment 1A. Again, there is no significant difference between RAND-REG and RAND throughout. Similar to that observed in Experiment 1, the difference between REG-RAND and

RAND-REG commences around 1020ms post-transition. Importantly, RAND-REG1 evokes a pupil dilation response which starts to become significant from 500ms post-transition, at approximately the same time as STEP, through to 1780ms.

Figure 5.2B shows the pupil response from the stimulus onset; as in Experiment 1 (Figure 3.1B), there is no appreciable difference between REG and RAND pre-transition.

Behavioural results

A repeated measures ANOVA shows no effect of condition on hit rates (Figure 5.2C; $F(2,22)=0.340$, $p=0.715$) or false alarm rates ($F(1.346,14.805)=1.878$, $p=0.177$, Greenhouse-Geisser corrected). As performance approaches the ceiling, a repeated measures ANOVA applied to arcsine transformed hit rates ($F(1.346,14.805)=1.878$, $p=0.192$, Greenhouse-Geisser corrected) and false alarm rates ($F(2,22)=0.386$, $p=0.684$) both show no effect of condition on task performance.

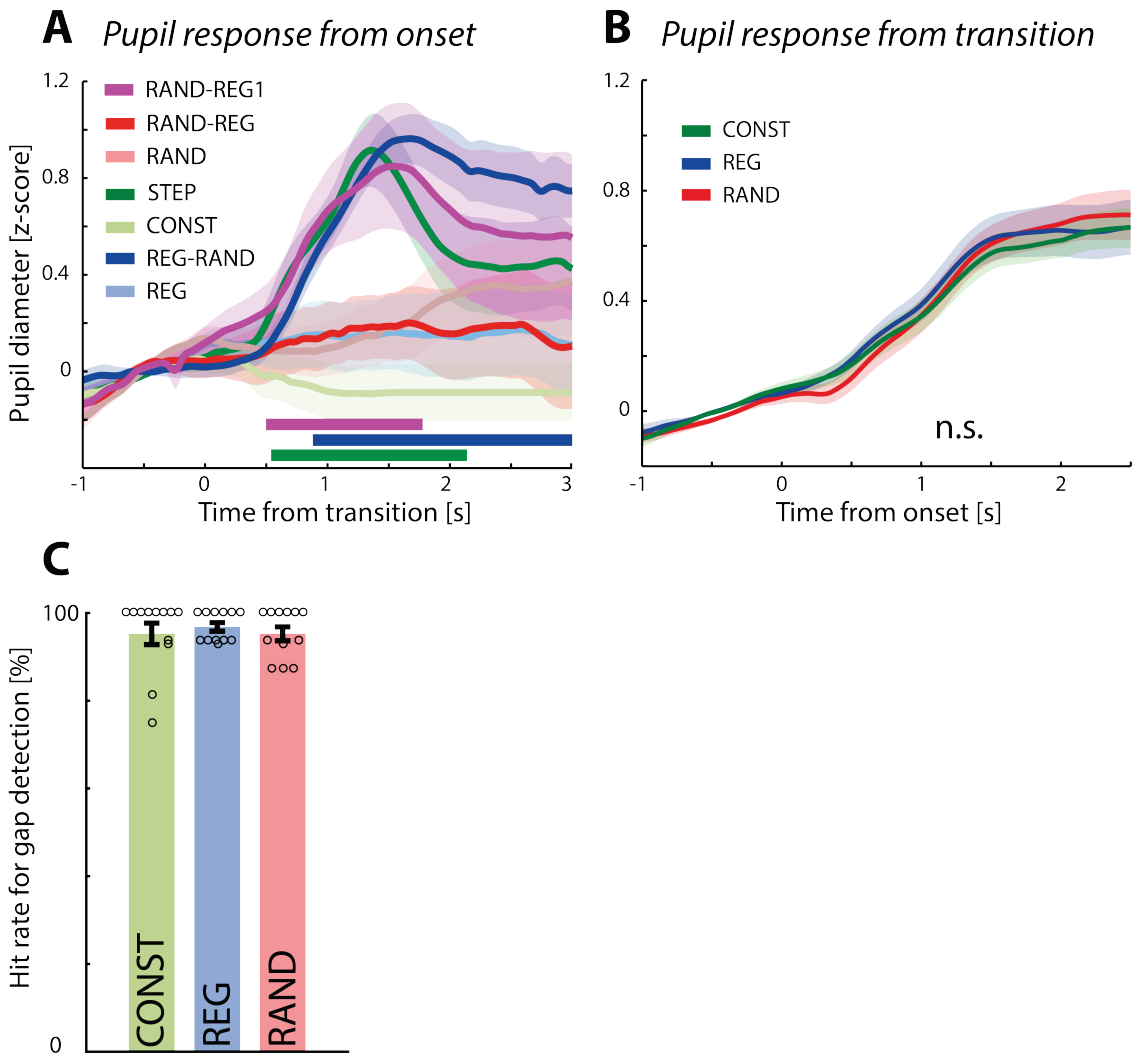


Figure 5.2 Pupil response and behavioural results of Experiment 3. [A] Average pupil diameter over time relative to the transition. The shaded area around the solid lines show ± 1 SEM. Time intervals in which cluster-level statistics show significant differences between each transition condition and their non-transition control ($p<0.05$) are indicated as identically-coloured horizontal lines below the plots. [B] Average pupil diameter relative to the stimulus onset. [C] Behavioural results for the gap detection task with 1 SEM error bars and black circles representing individual participant data.

5.2.3 Discussion

The result of this experiment has delivered further confirmation of the null-effect of pupil responses to the emergence of regularity (RAND-REG), reinforcing the observations of the previous two experiments. Additionally, the presence of an evoked pupil dilation response to the transition from a random sequence of 20 frequency-varying tones to a single tone repetition (RAND20-REG1) rejects the RAND saturation hypothesis.

Violation of randomness by repetition

At first, the presence of the pupil dilation response to the RAND20-REG1 transition may appear to be surprising as this could also be considered a form of the emergence of regularity. However, REG1 is an extreme case of regularity; it is merely a single repeating tone devoid of the spectral and temporal complexities present in RAND sequences. In addition to the discovery of a new pattern (repetition), the single repeating tone (REG1) also strongly violates the rule – 'the same tone appearing two or more times consecutively is rare' – implicitly conveyed in the complex random sequence pattern of RAND20.

The perceptual processing of stimuli depends on the context. In the context of a sequence of repeated standard tone, any noticeable deviation represents an unexpected event and elicits MMN, which has been thought to reflect a pre-attentive change detection system and supports the view of automatic rule extraction (reviewed in detail in Chapter 1; see also Garrido et al., 2009; Näätänen et al., 2007). However, in the context of permanently varying sequences, repetition represents an unexpected violation of the established permanent variation, and indeed, has been demonstrated to evoke an MMN-like response in numerous studies (Horváth et al., 2001; Horváth and Winkler, 2004; Näätänen and Rinne, 2002; Rosburg, 2004; Wolff and Schröger, 2001). This was first reported by Wolff and Schröger (2001): In a rapid tone sequence (presented at 6.25Hz) randomly sampling five different frequencies, rare repetitions of one tone elicited an MMN like negativity peaking about 100-200ms after the onset of repetition. This MMN like negativity is called 'repetition negativity' and found to be independent of attention (Horváth et al., 2001; Horváth and Winkler, 2004; Näätänen and Rinne, 2002; Wolff and Schröger, 2001). This has been interpreted as evidence for the ability of the auditory cortex to extract 'frequency variation […] as an invariant feature of the acoustic environment' (Wolff and Schröger, 2001, p323).

In this context, repetition leads to a strong unexpected error which can be observed as an MMN-like cortical response. The present study demonstrates that this strong violation

additionally activates the LC-NE system which leads to phasic NE activity, which, as demonstrated here, is observed as robust pupil dilation.

5.3 Experiment 4

5.3.1 Motivation

As shown above, the transition from a random sequence to a single repeating tone (RAND-REG1) evokes a clear and robust pupil dilation response, while the transition from a random sequence to a regular pattern with alphabet size 10 (RAND20-REG10) consistently produces no response. These observations lead to questions surrounding the characterization of the relationship between pupil responses and the tone subset size of the REG sequences, and how this subset size modulates pupil responses to the emergence of regularity (RAND-REG).

One possible result is that as the alphabet size of the emerging regular pattern progressively increases from one to ten, its evoked pupil responses gradually decrease in size before completely disappearing. Another possible result is that there is a categorical difference between REG1 and any other size; one repeating tone evokes a pupil dilation response on the principle that repetition is a special case of regularity. In this case, no pupil dilation response would be expected for any subset size greater than one.

To test which case is true, in addition to the RAND20-REG1 and RAND20-REG10 conditions which have been tested previously, the present experiment also includes two additional types of RAND-REG transitions: transitions from a random sequence to regular pattern with an alphabet size of two (RAND20-REG2) and five (RAND20-REG5) (see Figure 5.3 for examples). RAND20-REG2 is a necessary choice, as it can distinguish if there is a categorical difference between REG1 and other regular patterns. Also, the testing of the first hypothesis requires the examination of a range of subset sizes to cover the range of 1–10; an exhaustive approach would include the full range, however, experimental time constraints

permitted only two additional conditions: as such, RAND20-REG2 and RAND20-REG5 were selected as reasonable exploratory choices.

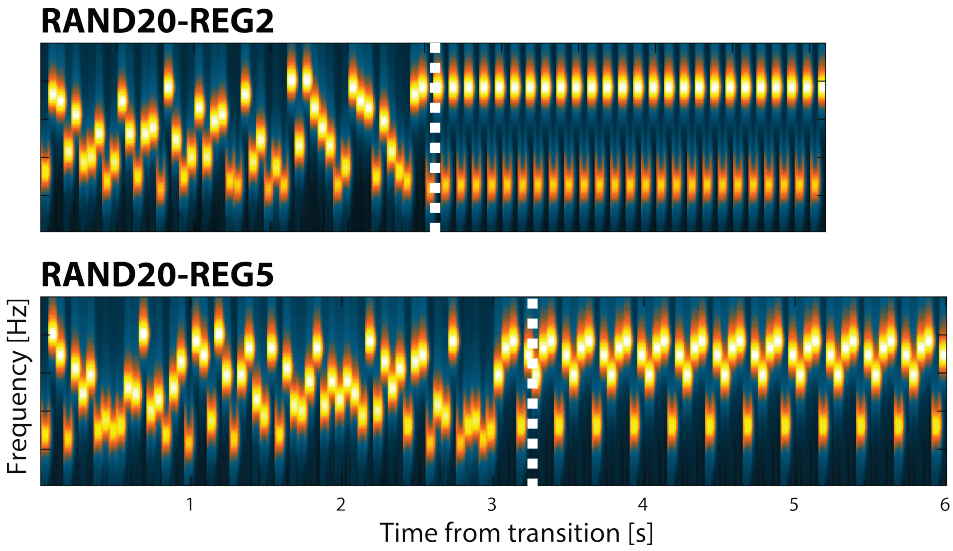


Figure 5.3 Example spectrograms for the stimuli RAND20-REG2 and RAND20-REG5. [Top] RAND20-REG2: a transition from a random sequence composed with tones varying across 20 different frequencies (RAND20) to a regular pattern with an alphabet size of two (REG2, i.e. restricted to two frequencies out of the pool of 20). [Bottom] RAND20-REG5: a transition from a random sequence to a regular pattern with an alphabet size of five.

5.3.2 Methods

Participants

This experiment was performed twice; a total of 30 new participants attended, with 15 participants initially and a new group of 15 participants subsequently, to replicate the results of the first attempt. Thus, participants are presented in two groups: the first 15 participants (11 females; aged 20–29, average 23.5) comprise Group A and last 15 participants (14 females; aged 20–25, average 22.5) comprise Group B. No participants were excluded in this experiment.

Stimuli and Procedure

In addition to the RAND20-REG1 stimuli of Experiment 3, two further stimuli were featured – RAND20-REG2 and RAND20-REG5 (examples shown in Figure 5.3). In this experiment, four transitions (RAND20-REG1, -REG2, -REG5 and -REG10) shared a single

RAND20 control, thus to ensure the same presentation probability across transitions and between respective transition and control conditions, the trial number should be same across all four transition stimuli and the RAND20 control count should be the sum of all transition trials.

Overall, 218 stimuli were presented, including 21 RAND20-REG1, 21 RAND20-REG2, 21 RAND20-REG5, 21 RAND20-REG10 and 84 RAND. Following the paradigm of Experiment 3, one-third of the sequences contained a gap, appearing with equal occurrence across conditions. All stimuli were shuffled and presented across seven blocks. Each block was around eight minutes followed by an eight-minute break.

5.3.3 Results

Average pupil diameter from stimulus transition

The results of Group A, the first 15 participants, are presented in Figure 5.4A. As in Experiment 3, RAND20-REG1 evokes a pupil dilation response, which diverges from its control RAND from 740 to 1700ms, while RAND20-REG10 shows no significant divergence from RAND20. The average pupil diameter in RAND20-REG1 starts to increase around 500ms post-transition and reaches peak amplitude at 1340ms. Moreover, the overall pupil diameter is significantly larger for RAND20-REG1 than RAND20-REG2 (between 1060 and 1620ms), RAND20-REG5 (780 and 1520ms) and RAND20-REG10 (620 and 1720ms).

There are no significant differences between RAND-REG2 or RAND-REG5 and their control, RAND. However, the average normalised pupil diameter in RAND-REG2 and RAND-REG5 appears to suggest a small gradual increase between 640ms and 800ms.

To investigate this further, the experiment was repeated with 15 fresh participants, who comprised Group B. Figure 5.4B shows the confirmation and replication of the results of their predecessors in Group A. RAND-REG1 diverges from RAND between 580ms and 1840ms, while RAND-REG2, RAND-REG5 and RAND-REG10 are not significantly different from RAND. Similarly, RAND-REG1 diverges from RAND-REG2 (between 740ms to 1660ms), RAND-REG5 (680ms to 1720ms) and RAND-REG10 (220ms to 1960ms).

Figure 5.4C shows pupil dilation responses obtained by pooling the two groups. In addition to the significant increase in RAND20-REG1 observed in the previous non-pooled results, the divergence of RAND20-REG2 from RAND20 becomes significant between 840ms to 1560ms post-transition. The pupil dilation to RAND-REG1 is significantly greater than the responses to RAND-REG2, RAND-REG5 and RAND-REG10.

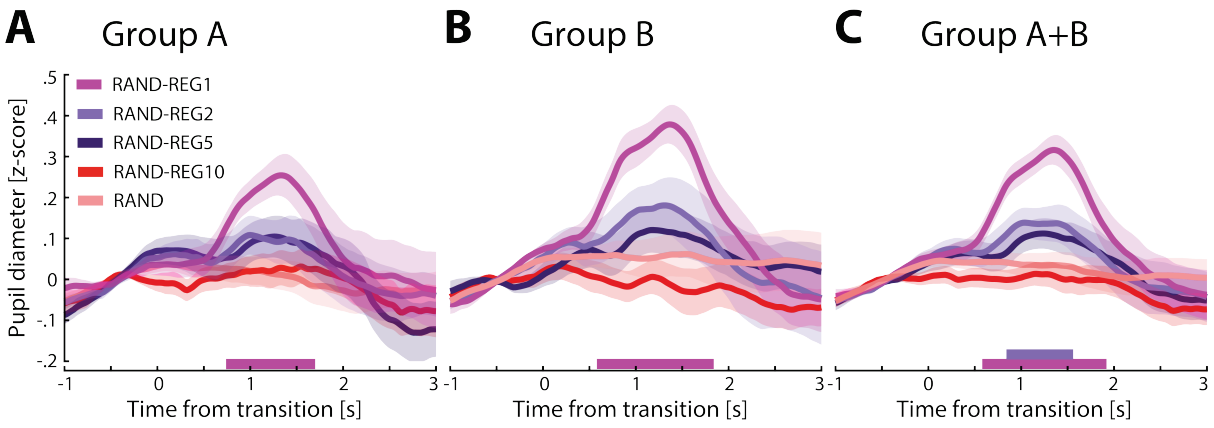


Figure 5.4 Average pupil diameter results for Experiment 4. Average pupil diameter over time relative to the transition: [A] Group A, (N=15), [B] Group B (N=15) and [C] both groups combined (N=30). The shaded area around the solid lines shows ± 1 SEM. The time intervals where cluster-level statistics indicate significant differences between each transition condition and the non-transition control RAND20 ($p<0.05$) are indicated as identically-coloured horizontal lines below the plots.

Pupil event rate from stimulus transition

Here the pupil event rates for all 30 participants in Experiment 4 are analysed in the same way as for Figure 3.4 of Experiment 1. The pupil dilation rate and pupil constriction rate results are presented in Figure 5.5 and Figure 5.6 respectively.

The left panel of Figure 5.5 shows the raster plot of the onsets of pupil dilations for each trial for all participants in Experiment 4. For RAND20-REG10, as in Experiment 1, there is no observable difference in the rate of pupil dilation onsets between RAND20-REG10 and its control RAND20. Likewise, there is no significant difference between RAND20-REG5 and RAND20 post-transition. Varying the threshold between 75ms and 300ms also reveals no discernible differences.

Contrastingly for RAND20-REG1, in agreement with its positive result in the average pupil diameter analysis, it exhibits a significantly higher rate of pupil dilation onsets 0.5 to 1-second post-transition ($p=0.01$) followed by a significantly lower rate from 1.5 to 2 seconds ($p<0.005$). This 'increase-then-decrease' pattern in the pupil dilation rate is identical to that of STEP and REG-RAND in Experiment 1.

A much less robust effect can be found in the pupil dilation rate of RAND20-REG2: with the threshold of 300ms, a significant reduction in the rate is apparent from 1.5 to 2 seconds ($p=0.02$); this effect disappears with a 75ms threshold.

For RAND20-REG5, both thresholds show no significant difference from RAND20 in the post-transition pupil dilation rate.

Regarding pupil constriction rate (Figure 5.6), again, RAND20-REG10 shows no change over the entire epoch, replicating the result in Figure 3.4. For RAND20-REG1, although there is no discernible indication of any rate change in the early post-transition interval, RAND20-REG1 shows a significant increase in the pupil constriction rate between 1.5s and 2s post-transition, though this is only significant with a 300ms threshold. This significant pupil constriction rate decrease matches the robust and significant pupil dilation rate decrease (Figure 5.6) and is similar to the pupil constriction rate result for STEP (with threshold 300ms) in Figure 3.4. For RAND20-REG2, like RAND20-REG10, there is no observable change in the pupil constriction rate. For RAND20-REG5, interestingly there is a weak but significant ($p<0.05$) increase in the rate between 1.5 and 2 second post-transition; this weak effect implies that RAND20-REG5 might indeed evoke some pupil responses, consistent with the grand mean waveform shown in Figure 5.4, albeit rather weakly.

Behavioural results

Task performance is very good across both groups: Group A with a hit rate (RAND20) of 94.8±2.0%, and false alarm rate (RAND20) of 0.2±0.1%; Group B achieved rates of 97.1±0.8% and 0.5±0.2% respectively.

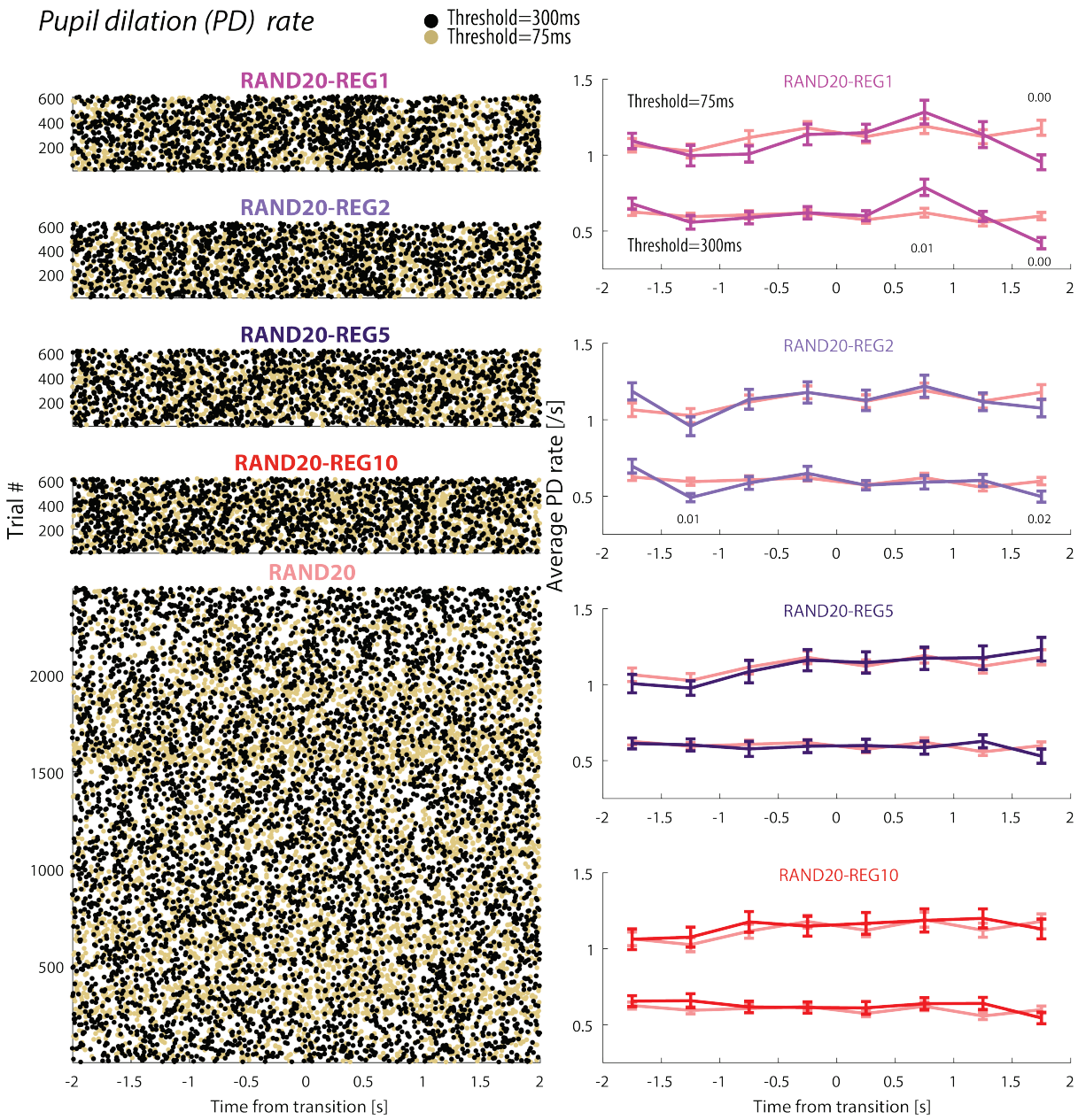


Figure 5.5 Pupil dilation rate results for Experiment 4 with participants pooled together (N=30). [Left] Raster plots of pupil dilation events extracted from all trials and all participants. Each black dot represents the onset of a pupil dilation with a duration exceeding 300ms, and each yellow coloured dot represents the same but with a shorter threshold length of 75ms. The black vertical line indicates the transition time. [Right] Average pupil dilation onset rate as a function of time relative to the transition for the two thresholds (from top to bottom: RAND20-REG1, RAND20-REG2, RAND20-REG5 and RAND20-REG10, all displayed against RAND20). Intervals with significantly different rates are labelled with asterisks with their associated p values.

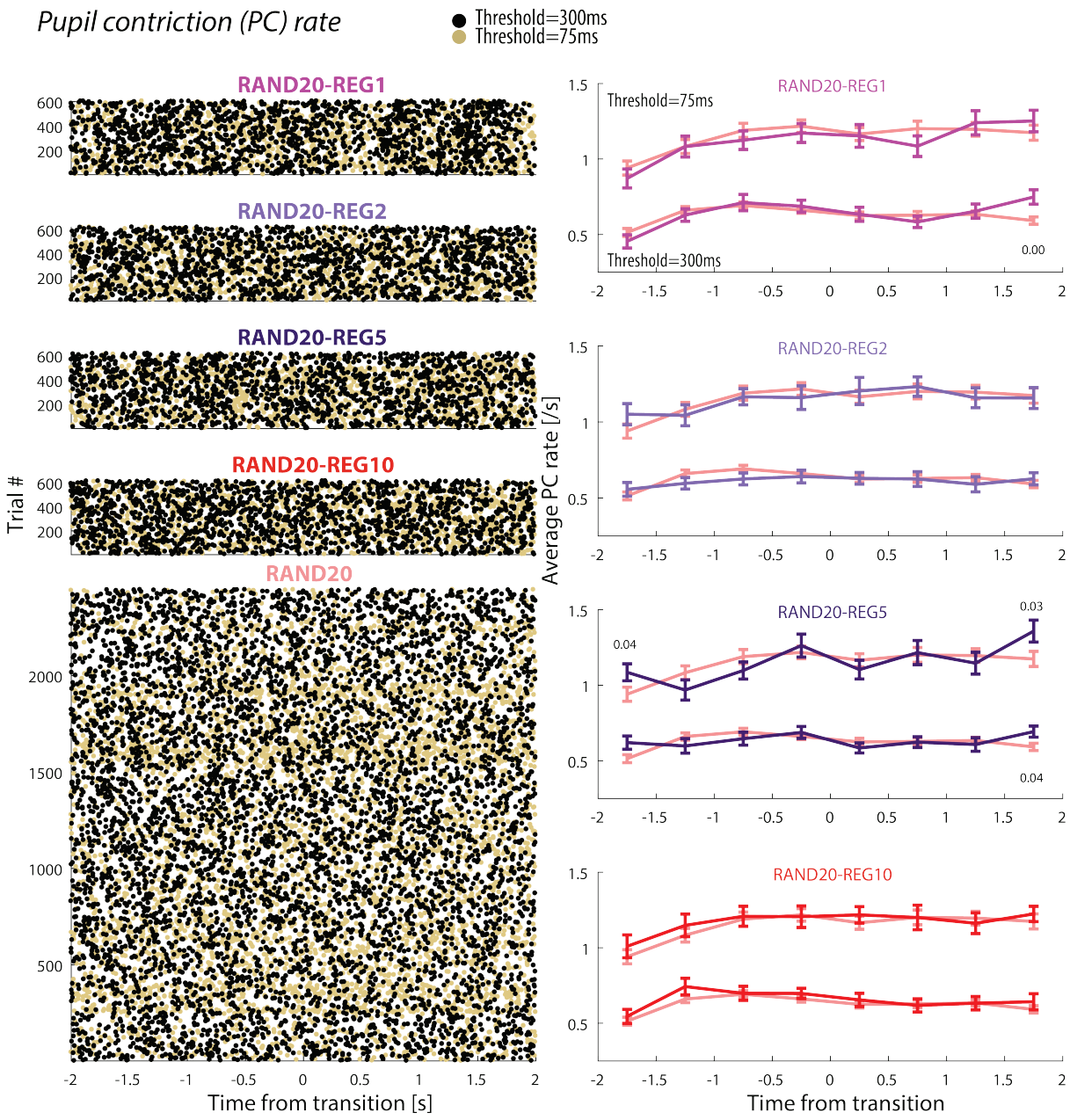


Figure 5.6 Pupil constriction rate results for Experiment 4 with participants pooled together (N=30). [Left] Raster plots of pupil constriction events extracted from all trials and all participants. Each black dot represents the onset of a pupil constriction with a duration exceeding 300ms, and each yellow coloured dot represents the same but with a shorter threshold length of 75ms. The black vertical line indicates the transition time. [Right] Average pupil constriction onset rate as a function of time relative to the transition for the two thresholds (from top to bottom: RAND20-REG1, RAND20-REG2, RAND20-REG5 and RAND20-REG10, all displayed against RAND20). Intervals with significantly different rates are labelled with asterisks with their associated p values.

5.4 Discussion

The experiments of this chapter have observed pupil dilation responses evoked by the violation of randomness by repetition: a transition from a random sequence to a single repeating tone, RAND20-REG1. This has been replicated twice and shares parallels with the responses elicited by the STEP and REG-RAND transitions. This positive result is also reflected in the pupil event rate analysis (Figure 5.5 and Figure 5.6), which show a significant increase shortly after the transition. This effect is only present in long-lasting pupil dilation events of over 300ms, and in all cases is followed by a significant decrease in the last time window (1.5 to 2 seconds) regardless of temporal threshold. There are two significant conclusions which may be drawn from these findings: firstly, the pupil response evoked by transitions from RAND20 categorically reject the hypothesis that the RAND-REG null effect observed in the last three chapters can be ascribed to pre-transition pupillary saturation. Secondly, the fact that RAND20-REG1 can also evoke a strong pupil dilation response provides further evidence that the LC-NE system is selectively sensitive to unexpected uncertainty; not only is the LC-NE system sensitive to violations of highly precise regularities, but also violations of complex randomness by mere repetition.

Moreover, the pupil dilation rate analysis for RAND20-REG1 shows slight inconsistencies across temporal thresholds for STEP and REG-RAND, an effect not observed in previous experiments with comparable participant and trial counts – 32 participants, approximately 500 trials per condition – where both thresholds show the same effect. This instability may suggest that the pupil responses to RAND20-REG1 are subtly different from those to STEP and REG-RAND. One possibility is that RAND20-REG1 evokes fewer pupil dilation events through the first second of the post-transition interval, or that the events have a slightly wider temporal spread, leading to a smaller resultant pupil dilation rate change, which was much less stable with slightly noisier data (when using a lower threshold for the pupil dilation duration). Another possible difference concerns the duration of the pupil dilation event itself; the increase in the rate for RAND20-REG1 disappears with a lower duration threshold,

which suggests that the increase in the pupil dilation rate by RAND20-REG1 is specifically associated with long-duration (lasting over 300ms) pupil dilation events.

In addition to the testing of the RAND20 saturation hypothesis, the present experiment further probes the effect of regularity complexity on pupillary sensitivity to the emergence of regularity by manipulating the size of the frequency subset of the regular pattern emerging from the random pattern. Here, in addition to the sizes of one (REG1) and ten (REG10) which have featured previously, the sizes of two and five are also investigated (RAND20-REG2 and RAND20-REG5 respectively).

Firstly, when increasing the regularity subset size from two, the pupil response to the random-to-regular transition almost completely disappears. This highlights the remarkable case of the violation of randomness by single tone repetition. Such a strong effect from the increase in subset size also agrees with the hypothesis that the LC-NE system is sensitive to the manner by which the rule describing the RAND20 portion – 'the same tone appearing two or more times consecutively is rare' – is encoded by the brain, in that REG1 offers the greatest possible violation of this rule. As the regular sequence increases in both complexity and length, this violation becomes progressively diminished, and is evidenced by a weakening in the response of the LC-NE system.

Nevertheless, there is some evidence that these two weaker transitions (RAND20-REG2 and RAND20-REG5) do evoke pupil dilation responses, albeit relatively much smaller; this is particularly apparent in the pooled data presented by Figure 5.4C. One hypothesis for this presence of pupil responses might be that when the regular cycle is relatively simple (i.e. with fewer than five members in the subset), the rapid recurrence of the short and simple cycles violates certain rule(s) learned from the RAND20 sequence; for example, in RAND20-REG2, the probability of a given frequency changes from 5% to 50% at the transition. Noticeably, compared with the RAND20-REG1 transition, the pupil dilation responses evoked by RAND20-REG2 (and RAND20-REG5) had significantly smaller peaks and tend to exhibit a more trapezoidal shape, with diminishing significance as the subset size grows. The underlying

reason for this graded trend in the pupil response strength from RAND20-REG1, RAND20-REG2 to RAND20-REG5 remains unclear. One possibility is that the evoked pupil dilation response (reflecting the phasic LC response) might be associated with the magnitude of the unexpected uncertainty and the evoked pupil dilation response (reflecting the phasic LC response); the stronger the violation, the greater the unexpected uncertainty (further away from the existing model of the ongoing sensory signal), leading to a stronger phasic LC response which can be observed as a larger pupil dilation response in the across-trial average result (illustrated in Figure 5.7). However, this hypothesis would only be true if two prerequisites are upheld: firstly, the strength of the phasic LC response is correlated with the strength of the unexpected uncertainty; secondly, the strength of the phasic LC response can be reflected by pupil dilation parameters (e.g. the amplitude of the pupil dilation, the spread of the pupil dilation onset time). Another possible hypothesis is that the activation of the LC-NE system has a greater variability across trials as the frequency subset size of the regular patterns increases. Taking RAND20-REG5 as an example, perhaps only a small portion of trials with this type of transition were strong enough to be considered a violation of the RAND20 sequence. The latter hypothesis is supported by the pupil dilation rate results: While there is a marked increase followed by a decrease shortly after in RAND20-REG1, the pupil dilation rate change was less significant and much noisier for RAND20-REG2, and completely absent for RAND20-REG5.

So far, the last four experiments in this thesis have demonstrated pupillometric results that support the initial hypothesis stated at the end of Chapter 1. Pupil dilation responses, as an index of phasic activity in the subcortical LC-NE system, are robustly evoked by transitions that involve strong violations of established rules in the ongoing sensory signal: violation by a deviant frequency by replacing one repeating frequency with another (STEP), violation of regularity by transitioning from a regular to a random sequence (REG10-RAND10), and violation of randomness by repetition (RAND20-REG1). Importantly, it is apparent that this response operates as an automatic process which does not require listeners to actively seek out the changes. Meanwhile, the process of discovering a new pattern does not evoke any

observable pupil responses; this is much unlike the results from the detection of a violation and reveals a separation between the networks involved in these two processes – detecting violations of learned rules involves the LC while the discovery of a new rule does not.

As all of these experiments are performed with listeners performing a task irrelevant to the transitions themselves, this raises intriguing questions: What if the listeners are actively searching for those changes? Are these networks – those responsible for violation detection, pattern discovery, and active searching for pattern changes – completely independent? How would the LC-linked pupil response be affected?

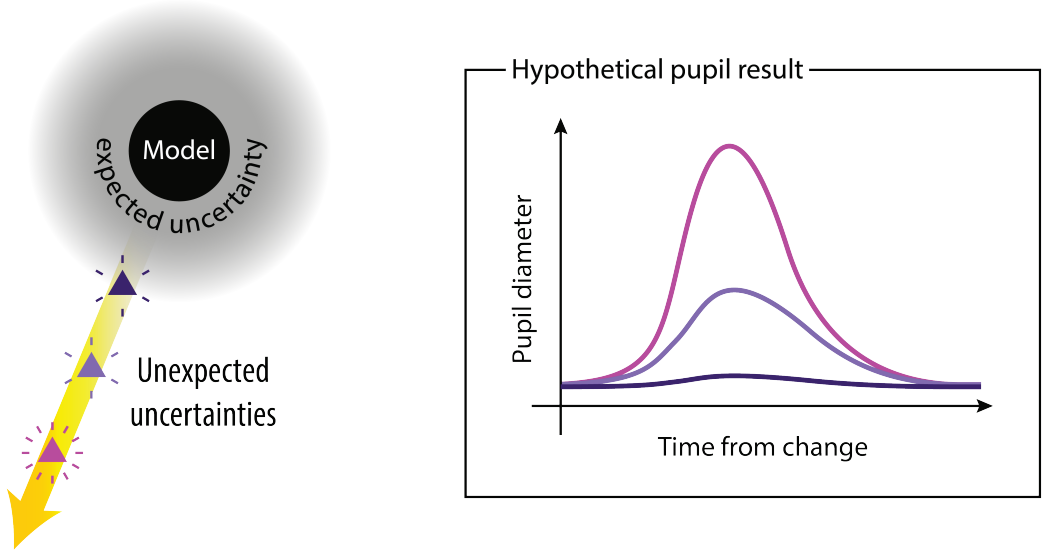


Figure 5.7 Schematics for a hypothesis about pupil responses to unexpected uncertainties with different strengths. [Left] Signals falling outside of the existing internal model (illustrated as a black solid circle with faded surroundings representing its expected uncertainty) would be considered as an unexpected uncertainty (illustrated as triangles). The further the unexpected uncertainty lies from the existing model, the stronger the unexpected uncertainty. In this diagram, the strongest unexpected uncertainty is indicated as a hot pink triangle, followed by light purple, and the weakest shown in dark purple. The hypothesis is that stronger unexpected uncertainties (further away from the existing model of the ongoing sensory signal) lead to a stronger phasic LC response. [Right] If this hypothesis is true, and the strength of phasic LC response can be observed as the amplitude of the pupil dilation response, then the pupil response (observed in across-trial averaging results) should increase in its size as the strength of the unexpected uncertainty increases.

6 How does behaviour affect pupil responses?

6.1 Motivation

The pupil responses which we have observed in the experiments described above demonstrate the LC's involvement in the tracking of rapid sequence statistics. A simplified cartoon of this process is illustrated in Figure 6.1A: Based on the available brain data, the tracking of the statistics of the sequences is hypothesized to take place in a network comprising sources in auditory cortex and IFG. Events which constitute unexpected uncertainty ('surprise') lead to activation of the LC, which is indirectly measurable as pupil dilation. Brain imaging experiments, with passive listeners, suggest that cortical pattern tracking takes place automatically. Changes in the pattern, both for REG-RAND and RAND-REG sequences appear to perceptually 'pop out', possibly once the evidence for a change has crossed some threshold. This aspect of the process remains poorly understood, but it is included in the schema for completion.

In this chapter, I investigate how introducing active detection would affect this network. This is important because indeed all previous studies, implicating LC-NE activity in the process of evidence accumulation used paradigms in which subjects were actively tracking and making perceptual decisions about the presented stimuli.

Pupil dilations have been observed during effortful behavioural, cognitive, or economic decisions (Aston-Jones and Cohen, 2005; de Gee et al., 2014; Einhäuser et al., 2008, 2010, Eldar et al., 2013, 2016; Fiedler and Glöckner, 2012; Gilzenrat et al., 2010; Hakerem and Sutton, 1966; Hess and Polt, 1964; Hupé et al., 2009; Jepma and Nieuwenhuis, 2011; Kahneman et al., 1967; Kahneman and Beatty, 1966; Nassar et al., 2012; Preuschoff et al., 2011; Privitera et al., 2010; Wierda et al., 2012). However, there is no clarity on which aspects of the decision-making process these responses reflect, and how they contribute to the associated pupil dilations.

One aspect known to have a profound effect is the final decision terminating the process. For example, Einhäuser et al., (2010) observed a significant correlation between the timings of the peak pupil dilation and the button-press on a single-trial basis, confirming a tight link between the timings of the two events. However, it is difficult to determine if these changes can be attributed to the decision-making process, or the motor preparation and command needed to report the decision, or perhaps a combination of the above processes amongst others.

The issue is complicated by the observation that the start of the pupil dilation occurs before the button press (Einhäuser et al., 2008, 2010; Hupé et al., 2009). With pupil responses aligned at the button press time, the pupil diameter starts to increase around one second before the button press, peaking at 420ms after the press, before resolving back to the baseline at two seconds after pressing; this response shows a degree of consistency across different studies (Einhäuser et al., 2008, 2010; Hupé et al., 2009). However, a slightly later pupil dilation onset, starting at 500ms and becoming significant from 400ms before the button press, was reported by Hupé et al. (2009). This difference in the pupil dilation onset can be attributed to the level of the task demand in these two studies. Pupil diameter is positively correlated with processing load (Beatty, 1982; Hess and Polt, 1964; Kahneman et al., 1967), and as such, pupil dilation starts earlier and rises more rapidly in trials with demanding tasks (which also tend to be associated with a longer reaction time).

To further explore the pupil response component of motor command and preparation, Hupé et al. (2009) investigated pupil dynamics in different change-detection button-pressing tasks with visual stimuli, including a mixture of active and passive tasks, and one where participants could press the button at will. In line with expectations, the active change detection tasks elicit pupil dilation responses with button presses, but intriguingly, consistent and reliable pupil dilation responses are also observed when participants press the button at will. Considering the LC's proposed role in behavioural optimisation (Aston-Jones & Cohen, 2005) and its projection to the Edinger–Westphal (EW) nucleus which controls the sphincter muscles which in turn constrict the pupil (Kozicz et al., 2011), a tight coupling between pupil dilation and motor responses is not at all surprising.

In addition to this, the relationship between pupil dilation and the actual choice made in the decision is also very interesting. Pupil measurements during visual detection tasks report larger dilations for hits than misses (Hakerem and Sutton, 1966; Privitera et al., 2010). Moreover, average pupil dilation amplitudes are significant bigger when responding with 'yes' than with 'no', while there is no discernible difference between the actual correctness of the response (de Gee et al., 2014); this is further evidence that the final choice of the decision process contributes heavily to decision-related pupil dilations.

In this case, with the decision formation process reflected in the pupil dilation response, one solution to disentangle the two could be to stretch the decision-making process over longer timeframes, for example, a decision based on a slow trickle of noisy information. de Gee et al. (2014) used a visual contrast detection task with long reaction times (typically around two seconds) and individually adjusted the task to attain a rate of 75% correct responses. With this, pupil responses were modelled using a general linear model with an impulse response function adopted from Hoeks and Levelt (1993), finding that the sustained component during the decision formation significantly contributed to the time course of the pupil response. Although the existence of the sustained component indicates evidence accumulation, it is still very difficult to precisely extract and quantitatively measure this component to extract any

further details about the evidence accumulation process. As such, dissociating evidence accumulation from other factors associated with the decision remains unsolved and requires further investigation.

From these findings, it can be seen that various aspects of behaviour – even the mere button press – can affect pupil responses. However, it remains unclear how these behavioural effects act on the automatic pupil response to the pattern transitions.

The paradigm in the present study is the same to that described in the experiments above except that now participants are instructed to monitor the sounds sequences for the transition and respond as quickly as possible when a transition has been detected. Figure 6.1B illustrates for a hypothesized sequence of operations which might be involved in this task: Once aware of the ongoing signal, listeners need to make the decision to respond and then execute the motor response (“press button”).

There are at least three manners in which active behaviour might affect the observed pupil response and these are schematized in (Figure 6.1C). One possibility (Figure 6.1C(i)) is that the behaviour-related neural network (including the direction of attention to the changes, making the final decision, executing the motor response etc) is completely independent from the AC-IFG-LC network. If this is the case, then pupil responses to the violation of regularity should be unaffected by behaviour: The results should be the same as those for the auditory gap detection task of the previous chapters. The second possibility (Figure 6.1C(ii)) is that the behaviour-related network (deciding whether to press the button, and the motor command itself) affects pupil responses, but independently from the statistical tracking network. If this is the case, the pupil response should be a combined response reflecting the behavioural response and the automatic response to the violation of regularity. Here, the pupil responses should exhibit two major features: (1) the responses to all three transitions should correlate with reaction times, and (2) the pupil responses to RAND-REG may be different, and possibly smaller, than those to STEP and REG-RAND and may also show greater correlation with reaction times as it only consists of components associated with the behavioural response.

Another possibility (Figure 6.1C(iii)) is that behaviour substantially affects the statistical tracking network and/or LC, resulting in pupil responses which cannot be not simply explained by behavioural responses.

In previous studies investigating the relationship between NE and unexpected uncertainty, active detection tasks were commonly used (Jepma and Nieuwenhuis, 2011; Krishnamurthy et al., 2017; Lavín et al., 2014; Preuschoff et al., 2011). For example, as reviewed in Chapter 1, Krishnamurthy et al. (2017) asked listeners to actively track sequences of sounds which vary spatially and predict the location of upcoming sounds. To accurately predict, the listeners need to actively learn the patterns underlying the distribution of sound locations and involve behavioural judgements to decide whether the pattern has changed or not.

However, there is a history of controversy over whether and how behaviour (e.g. final choice of the decision and the motor response itself) affects pupil responses. Thus, the next section presents a review of the literature regarding the effect of decision-making on pupil responses, as this would greatly assist understanding and interpretation of the results of the behavioural experiment.

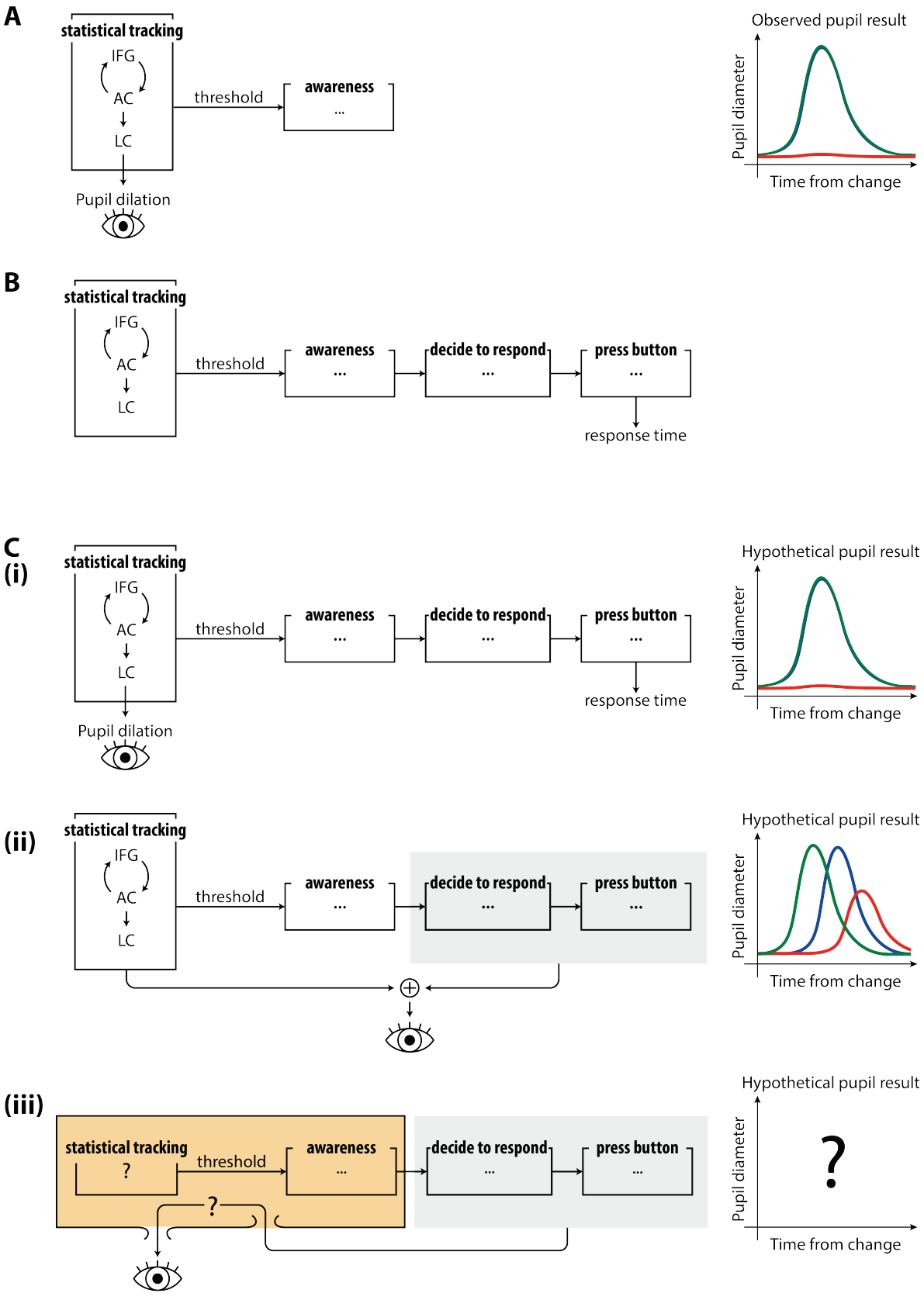


Figure 6.1 Schematics for hypotheses about pupil responses to pattern transitions. [A] illustrates a proposed mechanism for processing changes between regular and random patterns during passive

detection. The auditory cortex (AC) and inferior frontal gyrus (IFG) are proposed to act in tandem to detect auditory patterns contained within the rapid tone-pip sequence. The sensory signal reaches awareness if the statistics it carries pass a certain threshold. When the signal violates the incumbent internal model of the ongoing signal, the auditory cortex induces phasic neural responses in the LC which responds in turn, a response which can be observed as a transient pupil dilation response. The right-hand panel shows the observed pupil responses for STEP, REG-RAND and RAND-REG. [B] This is a simplified illustration of the hypothesis of a behaviour-involved transition detection process. When listeners are actively tracking and reporting the changes in sound sequences, the process should, at least, include five steps: track statistics in the sound sequence (by the AC-IFG-LC network), maintain awareness of a pattern, decide whether a change has happened or not, and finally execute the motor response. [C] proposes three possible manners in which active behaviour might affect the observed pupil response via the structure illustrated in [B]. See the main context for the details of each hypothesis. For each, the expected hypothetical pupil responses for STEP, REG-RAND and RAND-REG are illustrated on the right of each schematic.

6.2 Experiment 5

6.2.1 Methods

Participants

Data from 14 participants (10 females; aged 22–30, average 24.3) are presented. No participants were excluded in this experiment.

Stimuli

This experiment included the three transition conditions (STEP, REG-RAND, RAND-REG) and their corresponding non-transition controls (CONST, REG and RAND). The stimulus length was randomly varied between 120 and 160 tones (6–8 seconds), with the transition jittered between 60 and 80 tones after sequence onset.

Procedure

Participants were instructed to respond – by pressing a keyboard button – as quickly as possible after detecting a pattern change in the sound sequence; there were the transitions from one repeating tone to another (STEP), from a regular to a random sequence (REG-RAND) or from a random to a regular sequence (RAND-REG).

Experimental sessions typically lasted an hour, which included a short practice block of 12 trials before the main experiment. Again, as in Experiment 1, all six stimuli types featured

equally to avoid detrimental effects caused by unequal presentation probabilities. In total 150 stimuli were presented – 25 each of STEP, CONST, REG-RAND, REG, RAND-REG and RAND – all shuffled and presented with an inter-trial interval of five to seven seconds. To reduce fatigue, the stimuli were presented in five consecutive blocks and participants were asked to take a short break of around three minutes between blocks.

The analysis and plots are limited to three seconds post-transition as the earliest stimulus offset are at three seconds, and there is a slight increase in eye blink rate following stimulus offset.

6.2.2 Results

Behaviour: Rapid detection to complex sound patterns

Detection accuracy

Hit and false positive rates for the change detection task are presented in Figure 6.2A. Their similar hit rates show that all three transition conditions – STEP, REG-RAND and RAND-REG – can be equally detected by active listeners. A repeated measures ANOVA showed no effect of condition on the hit rate ($F(2,26)=0.258$, $p=0.774$) or on the arcsine transformed hit rate ($F(2,26)=0.198$, $p=0.821$). However there was a main effect of condition on false alarm rate ($F(1.394,18.118)=14.775$, $p<0.001$, Greenhouse-Geiser corrected) and on the arcsine transformed false alarm rate ($F(1.405,18.262)=15.272$, $p<0.001$, Greenhouse-Geisser corrected). Although the false alarm rates are all very low, RAND shows significantly higher rates (5.4±0.1%) than CONST (CONST=0±0%, $p<0.001$) and REG (REG=1.7±0.7%, $p=0.039$), while CONST and REG do not differ significantly ($p=0.083$; Bonferroni corrected).

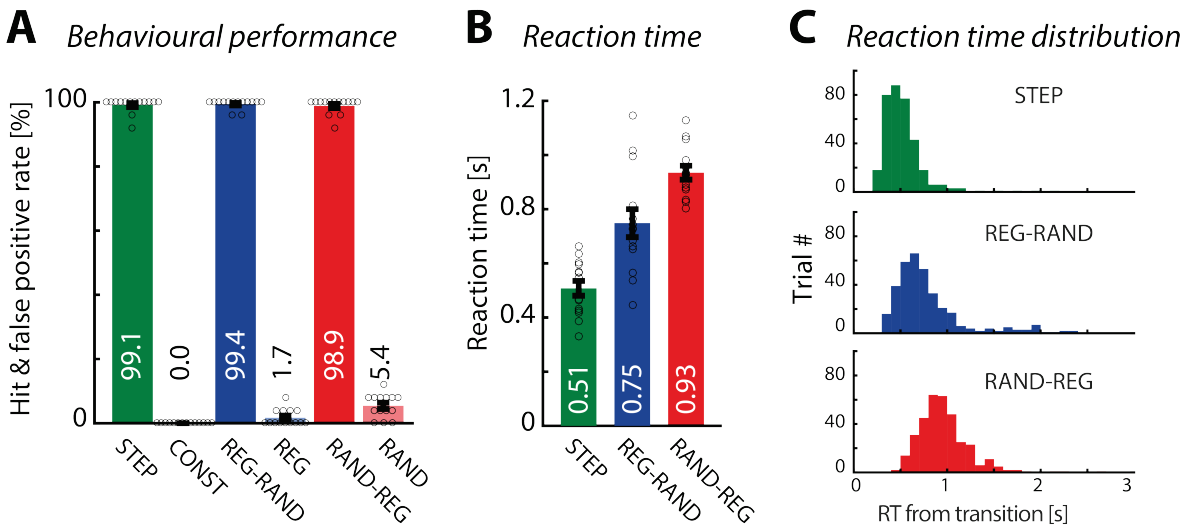


Figure 6.2 Behavioural results of Experiment 5. Behavioural performance of the active detection in STEP, REG-RAND and RAND-REG.[A and B] Hit rate, false positive rate and reaction times of the changes in STEP, REG-RAND and RAND-REG. Grey dots represent individual participant data. Error bars are 1 SEM. [C] The distribution of all reaction times (RT) for STEP, REG-RAND and RAND-REG are plotted.

Average reaction times

The reaction times (RT) in Figure 6.2B show that listeners detect these transitions very rapidly, on average within one second. A repeated measures ANOVA shows a main effect of condition on the reaction time ($F(2,26)=90.723$, $p<0.001$). The reaction time to changes in STEP stimuli are the shortest (RT=0.51±0.03s, $p<0.001$), followed by REG-RAND (0.748±0.05s, $p<0.001$) and then RAND-REG (0.93±0.03s, $p<0.001$). This latency pattern is consistent with previous work (Barascud et al., 2016), although reaction times are generally slower in the present study. This may be due to the participants' tiredness from constant fixation of the eyes and chin during the whole experiment.

Reaction time distributions

The distribution of reaction times for each change condition, shown in Figure 6.2C, are generally consistent with previous behavioural results (Figure 1.6, Barascud et al. 2016). Importantly, all reaction times occur considerably before stimulus offset, confirming that the stimulus lengths of this experiment are sufficient.

As mentioned in the discussion of Chapter 3, there is a possibility that the null-effect in RAND-REG during the gap detection task could be due to the wide spread of the reaction time

distribution. However, this experiment shows that the spread (variance) of the reaction time distribution of RAND-REG is smaller than that of REG-RAND (Levene's test, $F(1,690) = 14.426$, $p=0.0002$), thus providing further evidence that the null effect is not a mere artefact.

Average pupil diameters

Participants were instructed to listen for transitions in the tone sequences and press the button as soon as they detected the transition. From this, pupil responses to the pattern transitions can be investigated at three stages: stimulus onset, stimulus transition (external change), and the button press (time of decision).

Pupil responses from stimulus onset

Figure 6.3A shows the average normalised pupil diameter across all participants as a function of time, relative to the stimulus onset. As transition trials and their corresponding controls have common pre-transition sequences (i.e. CONST, REG and RAND), trials for each pair conditions can be collapsed for across-trial averaging.

In all conditions, the pupil gradually dilates from sequence onset. Following this initial increase, pupil responses to REG and RAND showed a continued increase with no apparent differences before the transition. In contrast, CONST stopped dilating, reaching a plateau around one second after onset. The divergence of CONST from REG was statistically significant at 1.98s post-onset, and divergence from RAND is significant from 1.92s post-onset until the transition. Therefore, in contrast to the previous experiments, here we observe a pre-transition disparity between complex frequency sequences (i.e. REG and RAND) and simple repetition (CONST).

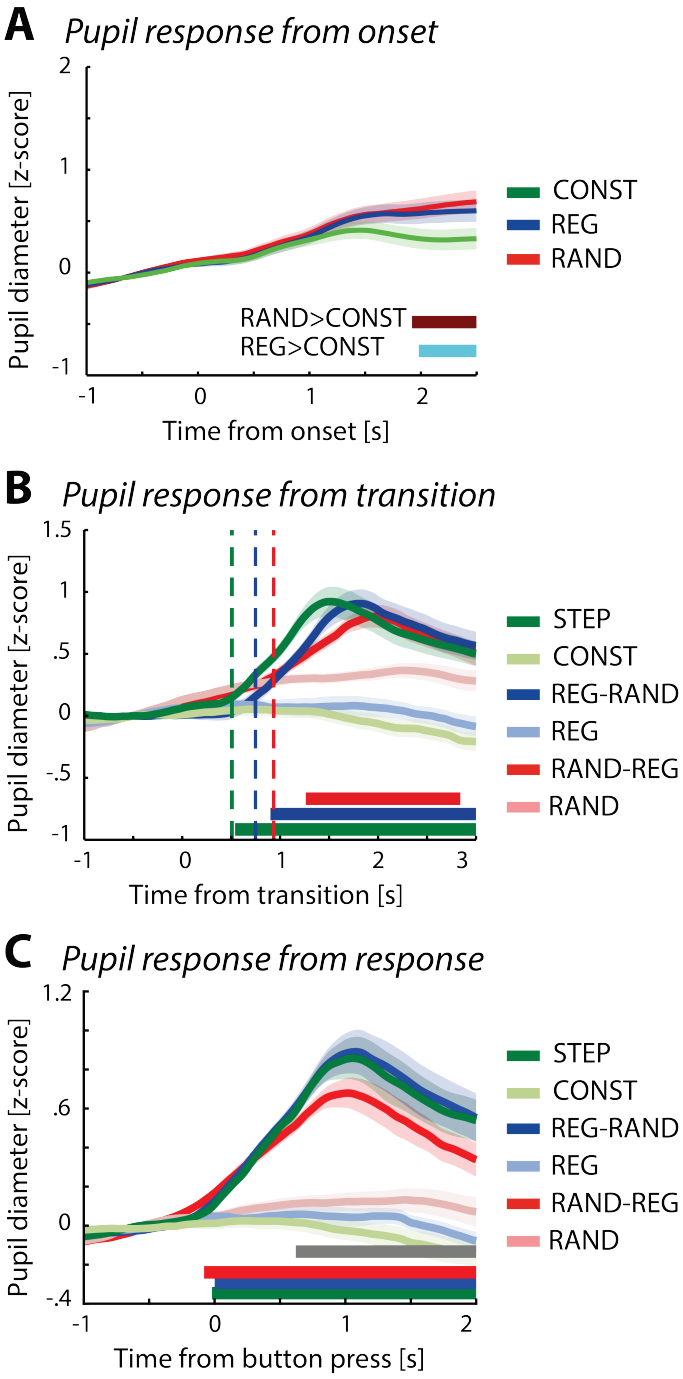


Figure 6.3 Pupil response results of Experiment 5. [A] Average pupil diameter over time relative to the sequence onset. The shaded area around the solid lines shows ± 1 SEM. The time intervals where cluster-level statistics show significant differences between each change condition and its no change control ($p<0.05$) are indicated by identically-coloured horizontal lines below the lines. [B] Average pupil diameter over time relative to the transition. [C] Average pupil diameter over time relative to the button press.

The underlying cause for this pre-transition difference remains unclear, but it may be related to the effect of effort on the pupil response. In the present study, the continuous repetition of a single tone in CONST may require less effort to track actively than the complex patterns of REG and RAND, thus resulting in smaller pupil diameters after the stimulus onset. A growing literature links the increase in tonic pupil diameter with increased perceptual and/or cognitive effort (Koelewijn et al., 2012, 2014, 2015, 2015, Zekveld et al., 2010, 2014). For example, (Koelewijn et al., 2012) found that listening to speech in the presence of an informational masker (e.g. a single-talker masker) evoked a larger pupil dilation response than in the presence of a masker with lower informational content (e.g. fluctuating noise). Another possibility is that larger pupil diameters reflect the expected uncertainty in complex frequency patterns. As reviewed in Chapter 1, ACh is proposed to signal expected uncertainty (Yu and Dayan, 2005) and has also been found to be related to non-luminance changes in pupil size, in particular with the sustained components of pupil responses (Krishnamurthy et al., 2017; Reimer et al., 2016).

Pupil responses from stimulus transition

Figure 6.3B plots the average normalised pupil diameter across all participants as a function of time, relative to the transition. Clear pupil dilation responses were observed in all three change conditions: STEP, REG-RAND and RAND-REG. Critically for this study, this was the first time a clear, robust pupil dilation response is associated with RAND20-REG10. The response started at 930ms, reaches its peak at 1980ms, and statistically diverged from its control RAND between 1260 and 2840ms. The response to STEP started to increase around 490ms post-transition, reaching peak amplitude at 1500ms; it statistically diverged from its control CONST from 540ms through to sequence offset. For REG-RAND, the responses started to increase around 750ms post-transition, peaking at 1840ms, and statistically diverged from its control REG at 900ms post-transition through to sequence offset. Comparing transition conditions directly, no difference was observed between the STEP and REG-RAND conditions, but the pupil diameter in REG-RAND became significantly greater than that in RAND-REG during 700ms and 1480ms post-transition.

Interestingly, it appeared that the onset of pupil dilation responses to each of the three transitions is in line with their corresponding average reaction times (as indicated by coloured dashed lines in Figure 6.3A). This implies that evoked pupil responses could have a strong link with decision-making process associated with transition detection. This will be further investigated with other analysis techniques.

Moreover, while the pupil dilation responses to CONST and REG generally remain constant post-transition, RAND sequences appeared to exhibit a slight continuous pupil dilation throughout (Figure 6.3B). As shown in Figure 6.3A, this difference did not emerge in the pre-transition period as no difference existed between REG and RAND. Importantly, this cannot be dismissed by the higher false positive rate of RAND, as trials with incorrect responses are excluded from analysis. This continuous pupil dilation throughout RAND sequences may reflect listening effort. Another possibility is that this increase in the sustained pupil response post-onset reflects the cholinergic response to the higher expected uncertainty of RAND (as discussed above; Krishnamurthy et al., 2017). However, the fact that this gradual increase in RAND was only observed during the active change detection task might favour the first listening effort hypothesis.

Pupil responses relative to the button press

Pupil dilations to the three change conditions started to rise away from their control at the mean reaction time (i.e. the time of the button press, indicated as coloured dashed lines in Figure 6.3B), showing a tight coupling between the button press and pupil dilation, which is consistent with studies on decision-related pupil dilations (see Einhäuser et al., 2010; Hupé et al., 2009).

To acquire a more accurate timing of the average pupil dilation relative to the button press, it may be useful to align pupil dilations with the button press; Figure 6.3C presents across-trial averages aligned at the time of the button press. All three transition conditions' pupil traces started to diverge from their controls around 200ms before the button press. The divergences started to be significant around the button press time; more precisely, STEP

deviated from CONST at 20ms before the button press, REG-RAND from REG at the button press, and RAND-REG from RAND at 80ms before the button press. RAND-REG was significantly lower than REG-RAND from 620ms after the button press. STEP reached a peak at 1060ms post-button press, REG-RAND at 1080ms, and RAND-REG at 1020ms.

Latency of peak pupil dilations (compared with the gap detection task)

Interestingly, the current experiment shows that the average pupil diameter response to REG-RAND reaches peak dilation later than in the previous experiments with the gap detection task. Examining the time that pupil dilation response reaches its peak of peak pupil dilations (peak pupil dilation time, or the time of the maximum pupil diameter, t_{max}) in group average results, the gap detection task experiments (Experiment 1A, Experiment 1B, the gap detection task session in the following two experiments Experiment 6 and Experiment 7) had t_{max} of STEP at around 1400ms (1520ms, 1400ms, 1440ms and 1420ms respectively), and t_{max} of REG-RAND at around 1400–1600ms post-transition (1640ms, 1400ms, 1520ms, and 1580ms respectively). However, in the present active change detection task experiment, the peak times of STEP and REG-RAND are at 1500ms and 1840ms respectively.

To compare the peak times between the two types of task, bootstrap analysis (1000 iterations and balanced; Efron and Tibshirani, 1994) was performed on two sets of participant data, one constructed from the 14 active participants of the present (5th) experiment and another from 57 passive participants pooled from Experiments 1A, 1B, 6 and 7. More specifically, this analysis involved randomly selecting (with replacement) 14 passive participants, computing their mean t_{max}, and then iterating 1000 times to create a population of *simulated* means for the passive group. The difference between the passive and active groups can be deemed significant if more than 95% of the simulated means fall above or below the mean of the active group (i.e. $p < 0.05$). Figure 6.4 presents this analysis of the peak dilation latency: violin plots show the distribution of t_{max} from the passive participants, and red crosses indicate the latency observed in the present experiment (active participants). The results

showed no difference (p = 0.3380) for STEP, but a significantly greater latency in the active task for REG-RAND (p = 0.0480, active = 2.000s, passive = 1.706s, difference = 294ms).

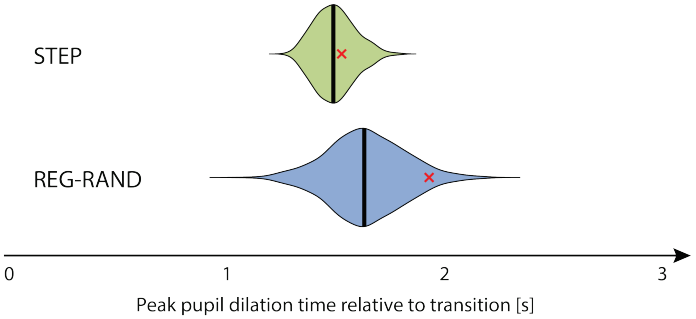


Figure 6.4 Comparison of peak pupil dilation time between the active change detection task and the gap detection task. The green violin plot shows the distribution of the 1000 stimulated means of the peak dilation latency of STEP from the 57 participants from the gap detection task experiments (Experiment 1A, Experiment 1B, Experiment 6 and Experiment 7) and the blue violin plot shows that of REG-RAND. The red crosses indicate the mean peak pupil dilation time of the active change detection task.

Relationship between reaction time and pupil dilation

To investigate the relationship between reaction time and pupil dilation response at a single-trial level, the trials were sorted by reaction time – the button press time – allowing better evaluation of the relationships between pupil dilation timing and the behavioural response.

Figure 6.5A shows the relationship between reaction time and pupil diameter over time relative to the transition time; the trials are sorted by the time of the button press (y-axis) and shown against the time relative to the transition time (x-axis). For display purposes, pupil diameter is z-normalized within each individual trial, instead of across trials per participant. Generally, pupil dilation occurred around one second after the button press (white line), which is consistent with Einhäuser et al. (2010).

This raises the question of whether the pupil dilation response observed here was merely a reflection of the button-pressing action. Figure 6.5B shows the correlation between reaction time and the peak pupil dilation time (t_{max}, see Figure 2.4 for illustration). A regression model of reaction time at t_{max} (based on rank scores) with participant as a random factor reveals correlations in REG-RAND ($t = 4.54$, $r^2 = 0.273$, $p < 0.0001$) and RAND-REG ($t = 4.83$, $r^2 = 0.362$, $p < 0.0001$), but not STEP ($t = 1.84$, $r^2 = 0.146$, $p = 0.0674$).

The relationship between reaction time and the derivative of the pupil dilation response is plotted in Figure 6.5D in a similar manner as in Figure 6.5A. Here, the pupil tended to dilate at higher speeds after button presses (yellow cluster to the right of the white line in Figure 6.5D). A regression model of reaction time by $t_{\Delta max}$ (ranked scores) with participant as a random factor showed no correlations in STEP ($t=0.58$, $r^2=0.0392$, $p=0.5648$) and REG-RAND ($t=-0.24$, $r^2=-0.0158$, $p=0.8123$), but a significant correlation in RAND-REG ($t=2.36$, $r^2=0.233$, $p=0.0190$) (Figure 6.5E).

Also investigated was the relationship between reaction time and the pupil dilation amplitude (i.e. the difference between the pupil sizes at the onset of the pupil dilation and the peak, see Figure 2.4 for an illustration). A regression model of reaction time by the pupil dilation amplitude (based on their rank scores, Figure 6.5C) with participant as a random factor showed

no correlation in all three conditions (STEP ($t=0.82$, $r^2=0.0657$, $p=0.4116$), REG-RAND ($t=-1.50$, $r^2=-0.103$, $p=0.1361$), RAND-REG ($t=-0.46$, $r^2=-0.0399$, $p=0.6441$)).

Overall, the single-trial analysis between RT and pupil dynamics showed that the effect of the behaviour differed across the three transition types: For STEP, there was no correlation between RT and t_{max}, or $t_{\Delta max}$. For REG-RAND, there was a small correlation, but only with t_{max}, not $t_{\Delta max}$, which suggests that although RT correlated with the pupil dilation response it only explained a small part of the variance. For RAND-REG, there were correlations with t_{max} and $t_{\Delta max}$, but the small r values reflected small variance explained.

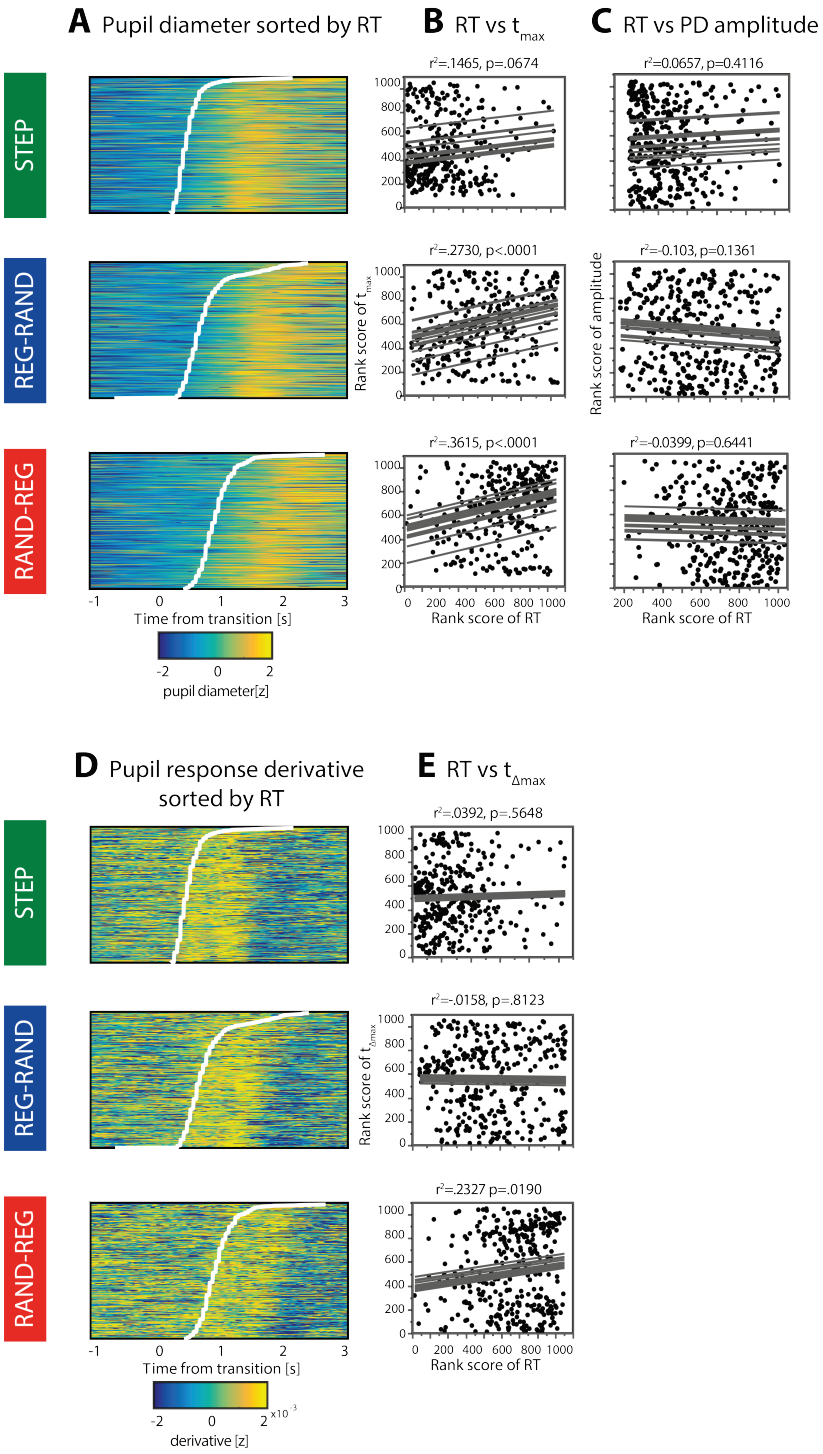


Figure 6.5 Relationships between the button-press and the pupil dilation response. Each transition condition is presented in a separate row: from top to bottom; these are STEP, REG-RAND, and RAND-REG. [A] Participants' trials sorted by their reaction time (RT) against time with relative to transient time, with the colours showing pupil size (the warmer the colour, the larger the pupil). The white line shows the button press time. For clarity, pupil size is z-normalised within trial, as opposed to across trials per participant. The colours in [D] represent the derivative of the pupil dilation response: the warmer the colour, the quicker the dilation. The correlation between the reaction time (RT) and [B] the peak time of the pupil dilation response (tmax), [C] pupil dilation amplitude, [D] the time of peak pupil dilation response derivative (tΔmax). Are plotted with their correlation coefficients presented above each graph; values for log(RT) were also

calculated but not shown, as the values are very similar to those presented here. The dots are individual trials and the lines are individual participants.

6.3 Discussion

All previous experiments of this thesis used a passive paradigm where pattern transitions were not relevant to the task performed by the participants. In contrast, the experiment featured in this chapter required listeners to actively seek and responding to the changes in the sequences.

Intriguingly, for all three transition types (STEP, REG-RAND and RAND-REG), the onset of the pupil dilation response – the moment the pupil diameter of the transition condition diverges from its no-change control – was at the same instant as the reaction time and peaks approximately one second later (Figure 6.3B). A similar relationship was evident in the average pupil diameter response aligned at the button press (Figure 6.3C). This is slightly inconsistent with Einhäuser et al. (2010), who found that the pupil diameter started to increase around one second before the button press and peaked at 420ms after the press. This may be due to differences in both the stimuli and analysis; Einhäuser et al. (2010) used a slow reward-related decision task (decision period of 10s) with no control pupil diameter response for comparison, thus dilation onset was defined as a positive zero-crossing, which, whilst maintaining commensurate peak times, would greatly affect onset timings.

To investigate the effect of the behaviour on the pupil dynamics, we also conducted a regression analysis on reaction time and three different parameters of the pupil dilation responses (time of maximum pupil diameter, amplitude of dilation, time of maximum dilation speed), on a single-trial basis. Although the regression analysis suggests a correlation between reaction time and pupil dynamics, this only exists when examining peak pupil dilation time and not the other two pupil dilation parameters (time of maximum dilation speed and amplitude of dilation); more importantly, the variance explained was small. This weak effect of reaction time on pupil dynamics suggests that these pupil dilation responses largely reflected

decision processes that were independent of the reaction time. In other words, these pupil responses were not merely driven by the motor response at the end of the active transition detection; they might be strongly driven by the decision formation or perceptual evidence accumulation processes (de Gee et al., 2014).

Overall experiment found three main consequences of the effect of behaviour on transition-associated pupil responses: (1) larger sustained pupil dilation even before the transition; (2) substantially later pupil dilation responses to the violation of regularity than during the previous auditory gap detection task; and (3) the appearance of pupil responses to the emergence of regularity. These are discussed, in turn, below.

First, during the pre-transition period, complex pattern sequences (REG and RAND) elicit greater pupil dilations than the single tone sequence (CONST). Particularly for RAND, this sustained dilation persists through to sequence offset, resulting in a larger overall pupil diameter than the other two no-change conditions. As mentioned in the result section, this is only present in this active detection experiment; although the basis for such sustained dilation is unclear, there are indications that it may reflect a greater effort when actively tracking complex pattern sequences.

Secondly, the introduction of active transition detection caused a delay (by ~300ms) to the pupil response to REG-RAND. The underlying reason for this delay remains unclear, but, together with the significant but small correlation between reaction time and peak pupil dilation time (Figure 6.5B) it may suggest that the pupil dilation response reflected a summation of two processes: the statistical tracking system, plus processes associated with the behavioural decision (as in the 2nd hypothesis, illustrated in Figure 6.1C(ii)). The latter underlies the correlation between the pupil dynamics and response time, but most of the unexplained variance was associated, with the statistical tracking network. Note that with the involvement of the behaviour, the statistical tracking network might be different from the AC-IFG-LC network under the passive listening condition, and this requires further exploration with functional imaging techniques. The single-trial analysis (Figure 6.5A) similarly showed that the pupil

dilation response followed the button press. The regression analysis on reaction time and pupil dilation parameters also revealed a significant correlation between reaction time and peak pupil dilation time (Figure 6.5B), providing further evidence for the link between pupil dynamics and the decision-making processes. However, it is noteworthy that this correlation between reaction time and pupil dynamics only existed in REG-RAND and RAND-REG. This echoes the findings of cross-task comparisons; while the peak pupil dilation time of REG-RAND was delayed during the active task, STEP was not affected by the task. It is possible that the simplicity of the change in STEP was associated with an automatic behavioural response, i.e. reduced decision making processes, and hence the pupil dilation response evoked by STEP more fully reflected the automatic change detection processes.

The third important finding concerns the fact that the RAND-REG transition - an emergence of regularity - evoked a transient pupil dilation response similar to that of the transitions in STEP and REG-RAND. This effect was observed for the first and only time in this thesis. Interestingly, and similarly to what was found for REG-RAND, reaction time showed only a weak correlation with the pupil dilation response (though the correlation was a bit larger than that observed for REG-RAND). Overall, this pattern of results favours the third hypothesis (Figure 6.1C(iii)): the LC-linked statistical tracking network is not behaviour-independent. Rather, it is subject to considerable influence by the involvement of active change detection (Figure 6.1C(iii)). The method of by which behaviour affects the process of signalling unexpected uncertainty in sensory signals cannot be further elucidated from the present pupil data, but future MEG and EEG studies comparing brain responses during passive and active listening could indeed develop further understanding. One hypothesis is that when participants actively seek changes from random to regular patterns, the brain stores internal representations for both types of pattern. Only once the statistical tracking network discovers and becomes aware of a new pattern, will it abruptly disconnect from the existing RAND model and switch for the other (REG) (as illustrated in Figure 6.6). Such disconnect-and-switch process might involve the LC-NE system, thus generating an associated pupil dilation

response. As this disconnect process might only happen after the new pattern reaches awareness, the timing of the pupil dilation response should also reflect the button press time. However, the time that takes to become aware and confirm an emerged new pattern depends on the details of the incoming patterns, which vary largely across trials. Such temporal variability across trials can be seen in the single trial MEG data shown in Figure 1.6 from Barascud et al. (2016), and it can partially explain the small effect of RT on the pupil response for RAND-REG observed in the present experiment.

Another possible explanation for the appearance of the response to RAND-REG is related to attention. When the brain actively directs attention to upcoming changes in the ongoing sequence, it is possible that any changes in the context – even if they are not violations of regularity – are amplified, thus making them sufficiently potent for the LC-NE system to report as an unexpected uncertainty event, which in turn becomes observable as a pupil response. Similarly, instead of amplifying the signals, top-down expectation-based signals might increase the sensitivity of the LC-NE system to changes deemed relevant to the task. However, many questions still remain: In what manner is the effect of behaviour (including attention) applied to pupil responses? Where does this effect act upon, e.g. IFG-AC loop for auditory pattern detection? Or the gating for the sensory signal to reach awareness?

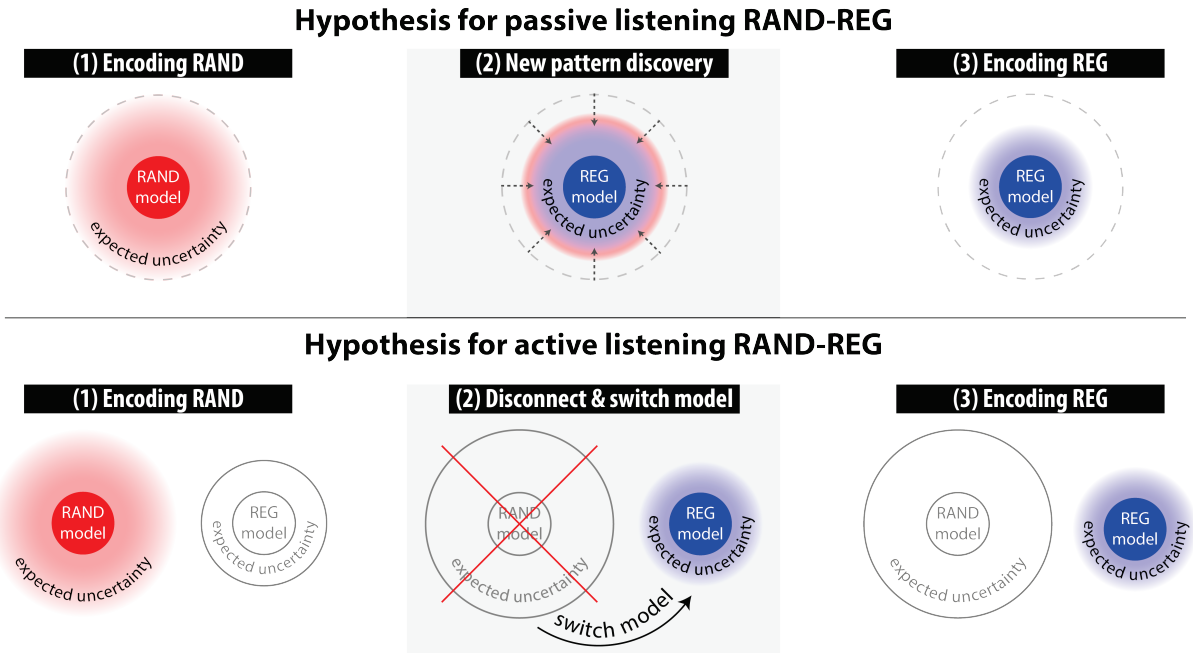


Figure 6.6 Schematic diagram for the hypothesis of active detection for the emergence of regularity (RAND-REG). The top panel shows the hypothesis of the process of RAND-REG, when listeners are performing an irrelevent task. Here three stages of the process are illustrated: (1) the internal model encodes the pattern while listening to the pre-transition sequence, and (2) after transition happened, as discovering the new pattern, the internal model gradually changes to represent the new pattern as the expected uncertainty reduces, (3) the new model is settled while continuing tracking statistics in the REG sequence. The bottom panel shows one of hypotheses of processing the same transition RAND-REG but during active listening condition. (1) As listeners have been explicitly told that there will be changes between two models - RAND and REG, even when listening to RAND, the listeners might keep a template for the model of REG. (2) After transition, once the brain discovers and becomes aware of a new pattern, it immediately disconnects from the existing RAND model and switches to the REG model. This stage might involve the LC-NE system, which leads to a pupil dilation response associated with RAND-REG observed in Experiment 5.

Overall, the work described in this chapter demonstrated that behaviour has a remarkably substantial and complicated influence on pupil responses to changes in rapid sound sequences. Considering the common use of change-relevant tasks in the past literature, the results and conclusions drawn from previous pupillometry studies in this field may well be limited to the LC-NE system under behaviourally influenced circumstances.

7 Effect of task

7.1 Introduction: Effect of task on deviant-evoked pupil dilation

The results of Chapters 3, 4 and 5 (featuring the gap detection task) show robust pupil dilations consistently evoked by unexpected pattern violations in rapid sound sequences, even when these events are not task relevant, supporting the hypothesis that phasic NE activity plays a critical role in the processing of unexpected changes in ongoing sensory information. This is consistent with previous studies showing that the pupil dilation response is sensitive to relatively rarely-occurring unexpected sounds (Liao et al., 2016b; Murphy et al., 2011, 2014; Qiyuan et al., 1985; Steinhauer and Zubin, 1982; Steinhauer and Hakerem, 1992; Wetzel et al., 2016). Moreover, the deviant-evoked pupil dilation response remains robust when participants are not voluntarily paying attention to the stimuli (Steiner and Barry, 2011; Wetzel et al., 2016) or even when distracted from the stimuli (Liao et al., 2016b). Overall, these findings agree with the expected roles of NE: changes in the ongoing sensory signal are automatically detected and processed to update internal representations, with phasic NE activity acting as a switch in this process, sending interrupt signals from the LC to the rest of the brain, including the areas engaged in higher-level cognitive functions, such as attentional processing (Sara and Bouret, 2012). Moreover, the MMN response to unexpected events has been recognised to be independent of attention and commonly thought to reflect an automatic process of the brain to track statistics and detect changes within the sensory signal. Thus, it is reasonable to hypothesise that the LC-mediated pupil dilation should be evoked independently of the

participants' task, and in other words, the evoked pupil dilation response should be task-independent; this chapter examines this hypothesis.

This is also supported by previous pupillometry studies which report that the deviant-evoked pupil dilation appears to be task-independent. Typically, this is tested with an auditory oddball paradigm. For example, in Liao et al. 2016b, participants were instructed to listen to a sequence of repeated standard stimuli (1000 Hz pure tone, separated by 300ms) imbedded with two types of deviant sounds (2000Hz pure tone and a brief white noise; stimulus probability <1.5%). In the active task, participants would be asked to report either immediately after detection by pressing a button (Liao et al., 2016b), or at the end of each block by providing a count (Steiner and Barry, 2011); both cases featured robustly evoked pupil dilation responses. In the passive listening task, participants would be asked to fixate at the centre of a screen without performing any other task (Liao et al., 2016b; Steiner and Barry, 2011; Wetzel et al., 2016), and it also featured the elicitation of oddball-evoked pupil dilations. However, there are some inconsistencies between studies: (1) Steiner and Barry (2011) found that larger pre-stimulus pupil diameters (by of around 0.1mm) observed during active listening (Steiner and Barry, 2011; Steinhauer et al., 2004) showed no significant difference from passive listening after baseline correction. However, in Liao et al. (2016b), the pupil dilation responses during active detection tasks were much stronger than those in passive listening tasks (for example, Figure 7.1B vs Figure 7.1D); this was hypothesized to reflect an enhancement in stimulus detection and response preparation processes. Moreover, Liao et al. (2016b) used two different deviants (2kHz pure tone and white noise) embedded in a repeating sequence of 1kHz pure tones, finding that only the white noise oddball evoked a small but significant pupil dilation (Figure 7.1B), while the 2kHz tone did not evoke any observable pupil response (Figure 7.1B). The difference in pupil dilation response could be a reflection of the difference in the content of the deviants: the perceptual difference between white noise and the standard tones is much greater than between the 2kHz tone and the standards. This is consistent with another study (Wetzel et al., 2016) which also observed the strongest deviant-evoked pupil dilation

with pink noise, followed by environmental sounds – such as crying babies and ringing phones – and finally frequency deviants. However, unlike Liao et al. (2016b), Wetzel et al. reported that frequency deviants also evoked pupil dilation; nevertheless, this effect was much smaller when compared to those evoked by other deviants (Figure 7.1A). This indicates that the null-effect of the pupil dilation in Liao et al. 2016b may be because the response to the frequency deviant is too small.

In addition to passive listening conditions, Liao et al. (2016b) also compared the effect on pupil dilation when participants were directed to attend to different modalities: audition or vision. In this study, participants were not only presented with auditory oddball stimuli, but also a sequence of visual stimuli displayed at the centre of a screen simultaneously. In the visual stimuli, standards were low spatial frequency patches, and deviants were high-spatial frequency patch and random-dot noise disks. These visual and auditory oddballs were presented asynchronously. No matter whether participants were detecting the auditory (Figure 7.1D) or visual oddballs (Figure 7.1C), auditory oddballs (red and blue solid lines) did evoke pupil dilations. This suggests that the effect of deviant-evoked pupil dilation response occurs irrespective of whether attention is focused on or away from the deviant stimuli. This is also in line with Koelewijn et al. (2009) who found that when attention was directed to a visual task, a noise burst attracted participants' attention and even affected visual task performance. This is associated with the P300 response, considered to be an electrophysiological index of the phasic NE response (Murphy et al., 2011; Polich, 2012) as P300 is also insensitive to the direction and participant of attention (Escera et al., 1998).

From this, the deviant-evoked pupil dilation response can be seen as a physiological index of the autonomic orienting response to the detection of a novel auditory event which deviates from the background (Liao et al., 2016b; Maher and Furedy, 1979; Nieuwenhuis et al., 2011; Sokolov, 1963), 'serv[ing] to enhance visual sensitivity' (Stelmack and Siddle, 1982, p706). In the present study, the STEP transition – a transition from repeating sequence of one single tone to another – features the introduction of a deviant frequency. If the evoked pupil

dilation response could be elicited regardless of tasks (like in Liao et al., 2016b) and is indeed a physiological index of the automatic orienting response, then, here, STEP should also evoke a pupil dilation response regardless of whether attention is directed towards audition or other modalities.

The studies in this thesis thus far have shown that the pupil dilates in response to pattern changes in sound sequences, irrespective of whether participants are asked to actively detect patterns changes themselves (cf. *non-active detection* in Chapter 3, 4, 5 and *active detection* in Chapter 6), suggesting that the activation of the LC-NE system does not require behavioural relevance. All experiments in Chapters 3, 4 and 5 employed a gap-detection task orthogonal to the transition of interest to ensure participants remain alert and awake while ensuring non-active detection. As such, to complete this examination of directed attention, the two experiments which follow intend to investigate the robustness of the pupil dilation response when directing attention to different modalities, for example, vision. This comparison of task-centric effects may further elucidate the underlying mechanisms of LC-mediated pupil dilations.

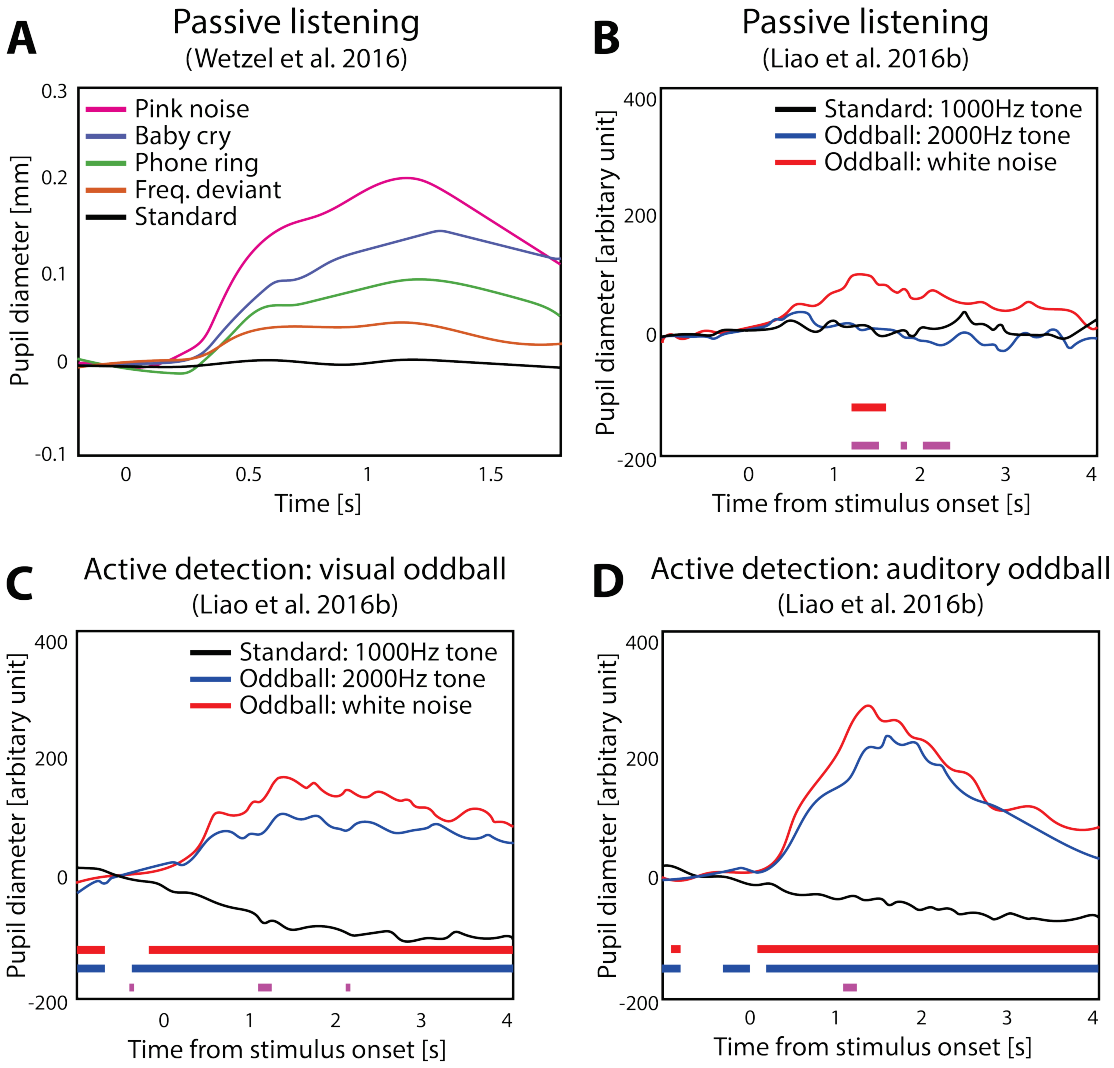


Figure 7.1 The deviant-evoked pupil dilation responses observed in previous studies. [A] Wetzel et al. (2016) presented participants with a sequence of repeating pure tones (standards) embedded with four different types of oddballs (frequency deviants, pink noise, 'phone ringing' and 'baby crying') and instructed to do nothing. The coloured solid curves represent the average pupil diameter as a function of time relative to the onset of the sound. In this passive listening paradigm, all oddball sounds were associated with a significant increase in pupil diameter. [B-D] present the results from Liao et al. 2016b, which also used an auditory oddball paradigm, with 1000Hz pure tones as standards (black solid line), and two types of oddballs: 2000Hz pure tones (blue solid line) and white noise (red solid line). The red and blue horizontal lines at the bottom indicate time intervals with statistical differences between the baseline (i.e. the response to the standard tone) and the oddball white noise (red) and the 2000Hz tones (blue) respectively. The purple horizontal line indicates the statistical difference between two types of oddballs. The time-series statistical test used a bootstrapping procedure with 1500 iterations for each time sample with the Bonferroni correction. [B] shows the pupil response to these sounds when participants were instructed to do nothing, like [A] in Wetzel et al. 2016. Here, a significant change in pupil diameter was only observed in the response to the white noise oddball. [C] Liao et al. 2016b also used a passive listening paradigm where participants were instructed to pay attention to a visual oddball sequence presented asynchronously with auditory oddball stimuli. The increase in pupil diameter was significant in response to both types of deviant. [D] In the active paradigm of Liao et al. 2016b, with the same stimuli, participants were instructed to actively report the auditory oddballs (white noise and frequency deviants). A robust evoked pupil dilation could be observed for both types of deviants. Adapted from Liao et al. (2016b) with permission.

7.2 Experiment 6

7.2.1 Methods

Participants

Data from 19 participants (14 females, aged 22-30, average 23.8) are presented. Chronologically, this experiment was performed after the next experiment, where over half of the participants were excluded due to their excessive blink rates. As a result, many more participants were deliberately recruited for this (6^{th}) experiment, as a similarly high exclusion rate was expected. However, substantially fewer participants were excluded, possibly due to differences between participants and growing experience in eye-tracking operation.

Stimuli and Procedure

As in Experiment 1, this experiment included all three types of transitions – namely the transition from one repeating tone to another (STEP), from a regular to a random sequence (REG-RAND) and from a random to a regular sequence (RAND-REG) – and their corresponding controls (CONST, REG and RAND). The stimulus length varied randomly between five and seven seconds, with a jittered transition time at around 2.5 and 3.5 seconds post-onset.

Two tasks featured in this experiment. The first was auditory gap detection, borrowed from Experiment 1A, with 16.7% of the sequences containing a gap partway through the sequence. The gap lengths were the same as for Experiment 1A: one tone missing in CONST and STEP, and two tones missing in REG, REG-RAND, RAND and RAND-REG. As this experiment preceded Experiment 1B, it did not feature the modified gap lengths of the later experiments. Nevertheless, as Chapter 2 showed, behavioural differences across conditions do not affect the pupil dilation response pattern observed in Experiment 1A. The other task was a visual background colour inversion. Instead of inserting a gap into the sequences, the monitor briefly inverted colours for 50ms before reverting – the black background became

white and the white fixation cross became black. As in the auditory gap detection task, 16.7% of the sequences contained a task-relevant target, equally distributed across conditions.

The visual background colour inversion was deliberately designed to balance redirecting attention while occupying minimal attentional resources. As in previous experiments, participants were instructed to respond – by pressing a button – as quickly as possible after detection. Importantly, any trials with gaps or with background contrast inversion and trials in which participants pressed a button were excluded from further analysis.

The two tasks were split across separate sessions and counterbalanced across participants. In addition to the trials that contained gap or background contrast inversion, each session contained 60 stimuli, 10 each of STEP, CONST, REG-RAND, REG, RAND-REG and RAND, all shuffled and presented in randomised order, with an inter-trial interval of six seconds. To reduce fatigue, each session was divided into two blocks, each lasting for around 10 minutes with 3–5 minutes break in-between. Each of the two blocks had a dedicated instruction and practise session to avoid confusion of the tasks.

Participant exclusion

To rule out the confounds of gaze positions and blinks on the pupil response across tasks, participants are excluded – using the same criteria and methodologies as before – if they excessively blink or gaze away from the fixation cross. From this, any participants with an above-average blink rate for any condition in any task are rejected, and in this experiment, two were excluded (see Figure 7.2A and Figure 7.3A for the average blink rates). In the present study, the gaze locations during the auditory gap detection task were used as the gaze criterion and were used to compute a three-standard-deviation gaze radius threshold (indicated as the red dashed rectangle in Figure 7.2B). This threshold was then applied to the gaze locations during the visual background colour inversion, and any participants with a mean gaze position beyond the threshold are excluded (Figure 7.3B). As all participants fixated well, no participants were excluded by this criterion.

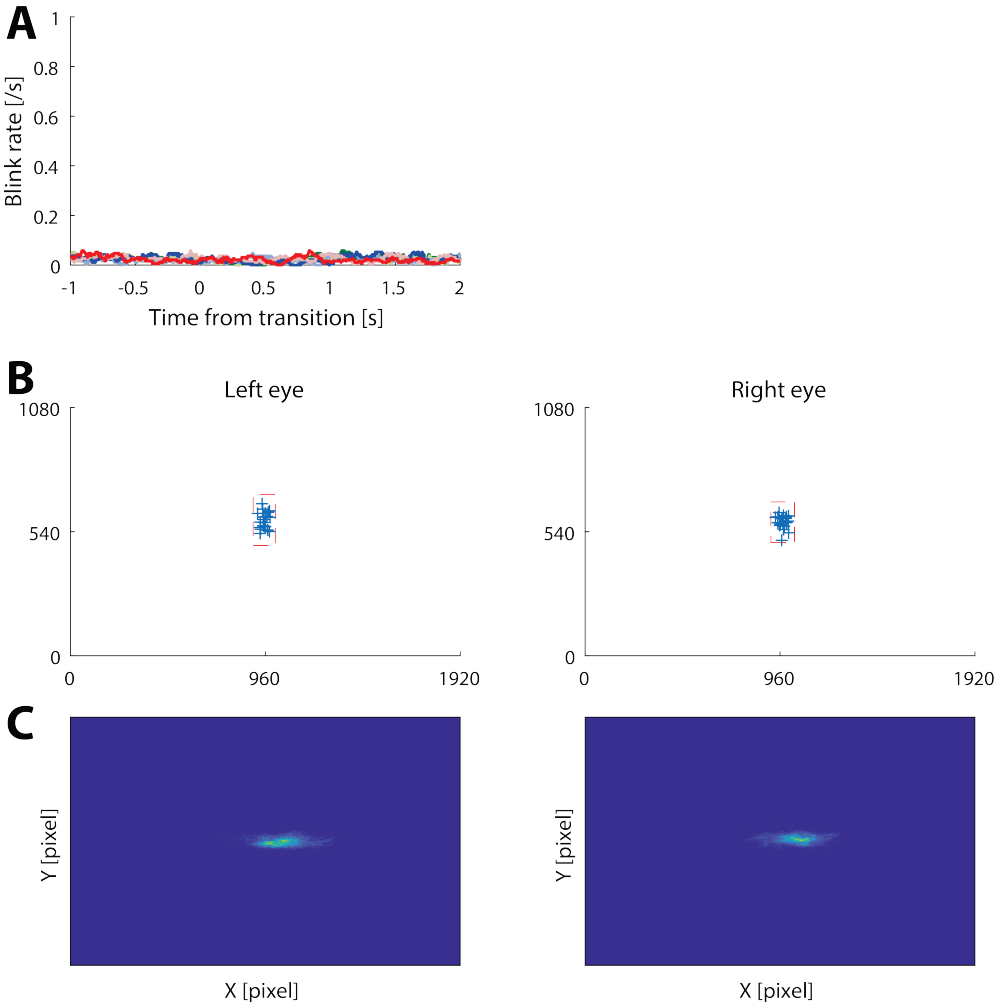


Figure 7.2 Blink and gaze locations in Experiment 6 during the auditory gap detection task (N=19).[A] Average blink rate (probability of occurrence) as a function of time relative to transition. [B] Gaze positions: The red dashed rectangle indicates the gaze radius threshold for this experiment, which is three standard deviations from the mean of all gaze positions in this task. Each cross represents the average gaze position for one individual participant during this task; blue colour means this participant's average gaze position is within the threshold. [C] Heat map for gaze positions from all participants and all epochs during this task.

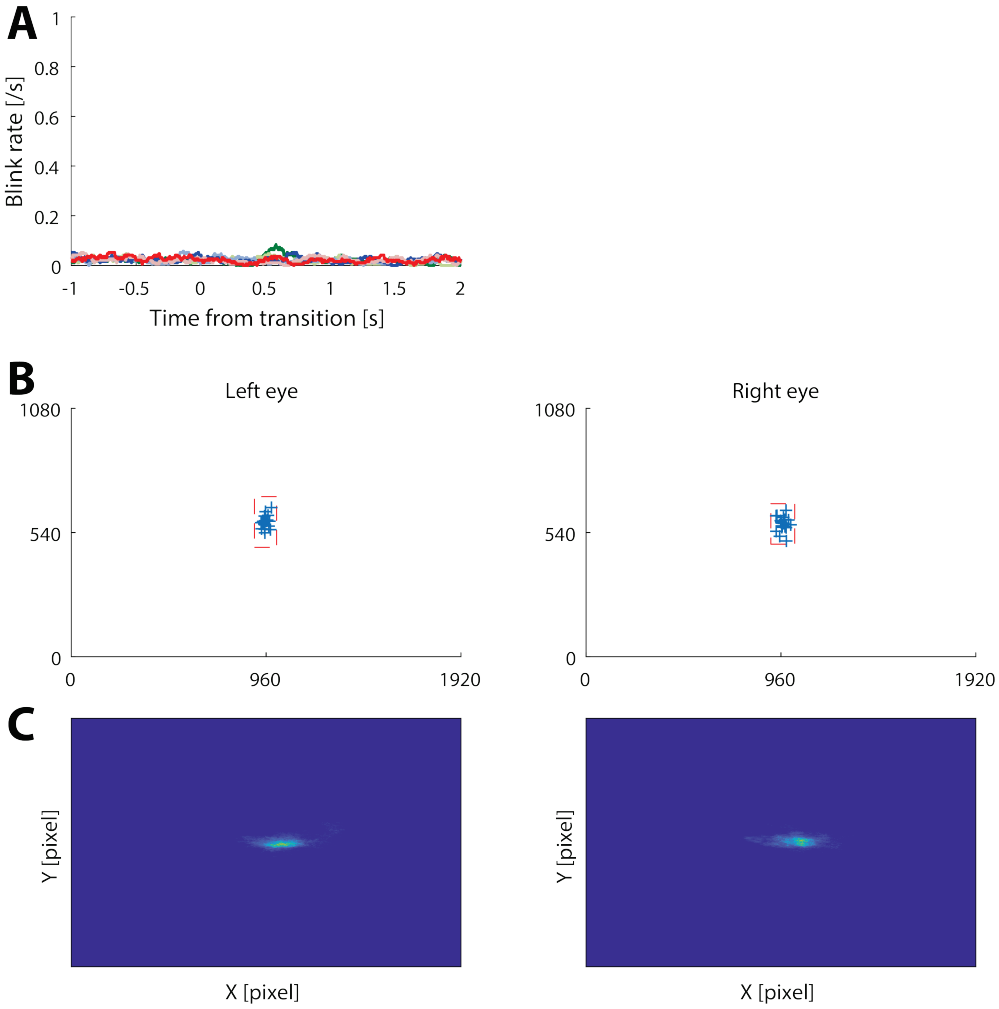


Figure 7.3 Blink and gaze locations in Experiment 6 during the visual background colour inversion task (N=19). [A] Average blink rate (probability of occurrence) as a function of time relative to transition. [B] Gaze positions: The red dashed rectangle indicates the gaze radius threshold for this experiment, which is the three-standard-deviation from the mean of the gaze positions in the auditory gap detection task in this experiment (Figure 7.2B). Each cross represents the average gaze position for one individual participant during this task; blue colour means this participant's average gaze position is within the threshold. [C] Heat map for gaze positions from all participants and all epochs during this task.

7.2.2 Results

Behavioural results

In terms of hit rate (Table 7.1), a two-way ANOVA examining the effect of condition and task on the arcsine transformed hit rate and shows no interaction between the effects of condition and task ($F(2,108)=2.501$, $p=0.087$), and no effect of condition ($F(2,108)=2.249$, $p=0.110$). However, there is a main effect of task on the arcsine transformed hit rate ($F(1,108)=4.197$, $p=0.043$), suggesting that the visual background colour inversion task has a better overall performance than the auditory gap detection task.

Examining arcsine transformed false alarm rates (Table 7.1) shows no interaction between condition and task ($F(2,108)=1.459$, $p=0.237$), and neither task ($F(1,108)=1.095$, $p=0.298$) nor condition ($F(2,108)=1.459$, $p=0.237$).

	Hit Rate [%]			False Alarm Rate [%]		
	CONST	REG	RAND	CONST	REG	RAND
Auditory gap detection	97.4±2.6	86.8±5.2	78.9±7.9	0±0	2.1±1.0	1.1±0.7
Visual background colour inversion	97.4±2.6	100±0	100±0	0.5±0.5	0.5±0.5	0.5±0.5

Table 7.1. Behavioural result hit rate and false alarm rates for the two tasks of Experiment 6 (N=19). Uncertainties are ±1 SEM.

Average pupil diameter relative to stimulus transition

Figure 7.4 shows the pupil dilation response from transition for the two tasks. Once again, the pupil dilation response pattern observed in Experiment 1 has been replicated: For the auditory gap detection task (Figure 7.4A), STEP (640–2000ms) and REG-RAND (800–2000ms) show pupil dilations, while RAND-REG does not. As previously, the response to REG-RAND is significantly higher than that to RAND-REG from 1200 to 2000ms. For the visual background colour inversion task, no pupil dilation response is apparent for any change conditions (Figure 7.4B).

Here, the pupil response effect completely disappears when attention is directed towards a visual modality; even the simplest pattern transition from one repeating tone to another (STEP) evoked no observable pupil dilation.

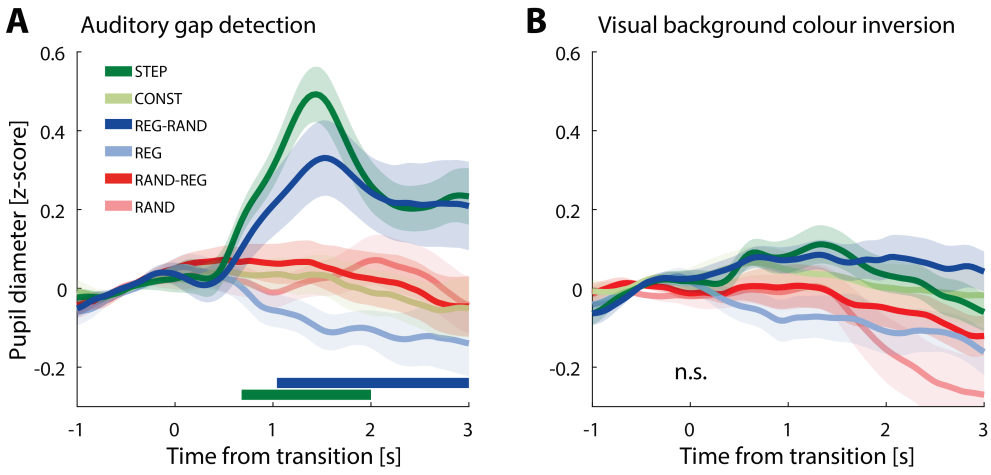


Figure 7.4 Pupil response results for Experiment 6. The solid line represents the average normalised pupil diameter over time relative to the transition for the two tasks: [A] the auditory gap detection task and [B] the visual background colour inversion task respectively. The shaded area shows ±1 SEM. Identically-coloured horizontal lines below the plots indicate time intervals where cluster-level statistics showed significant differences between each change condition and its no change control ($p<0.05$).

7.3 Experiment 7

7.3.1 Motivation

The null-effect of pupil responses during the visual background colour inversion task observed in Experiment 6 is both very surprising and important, one which this experiment seeks to replicate and confirm with a new participant group. It also raises the question of whether any non-auditory task would result in a similar lack of pupil dilation, so in addition to the familiar visual task, this experiment also introduces a tactile task. Another interpretation of that finding is that the only requirement for the deviant-evoked pupil dilation response is that participants must pay attention to the sound, but the manner of this attention is inconsequential. So far, the findings show that observable pupil responses can be produced by the auditory gap detection task, in which participants must actively and continuously monitor for gaps. Then, what if participants are attending to the auditory sequence without continuous tracking? Would

changes in the sequence still evoke observable pupil dilations? To assess these questions, this experiment introduces an additional task – auditory noise burst detection – in which a small proportion of stimuli feature a brief burst of white noise in a random position. Therefore, the data of four different tasks are be presented in this final experiment of the thesis.

7.3.2 Methods

Participants

Data from six participants (3 females, aged 21-23, average 21.8) are presented. In total 16 participants attended this experiment, but six participants were excluded due to excessive blink rates and additional four participants were excluded due to gazing away from the centre of the screen (details see Participant Exclusion).

This experiment was performed at NTT Communication Science Laboratories, in Atsugi, Japan. The experimental procedures were approved by the NTT Communication Science Laboratories Ethical Committee. Each participant provided written informed consent and were paid for their participation. All reported normal hearing, normal or corrected-to-normal vision, and no history of neurological disorders. In this thesis, this is the sole experiment conducted outside UCL.

Stimuli and Procedure

As in Experiment 7, each task contained 60 stimuli – 10 each of STEP, CONST, REG-RAND, REG, RAND-REG and RAND – which were presented in random order. Each task was contained in its own block and thus the whole experiment contained four blocks, with the task order randomised and counterbalanced across participants.

The four tasks are as follows:

A. **Auditory gap detection**: As in Experiment 6.

B. **Visual background colour inversion**: As in Experiment 6.

C. **Auditory noise detection**: A 50ms-long noise was occasionally inserted into the sequences. The noise was generated with a bandpass Butterworth filter between 3 and 12kHz (sampling rate 44.1kHz). The same noise was used for all participants.

D. **Tactile vibration detection**: A tactile stimulus was inserted as a detection target. This was presented to the participant's left hand as a passive vibration, with a sine wave carrier frequency of 250Hz and duration of 300ms.

These tasks are deliberately simple to only sufficiently redirect attention while occupying minimal attentional resources. Participants were instructed to press the button as quickly as possible once they detect the target (gap, background colour change, noise burst or tactile vibration, depending on the task). As in Experiment 6, to avoid confusion and misunderstanding about the tasks, instruction and practice was given at the beginning of each block. Within each block, two trials of each condition contained a target. As in previous experiments, any trials containing a target (gap, background colour change, noise burst or tactile vibration – depends on the task) or trial in which participants pressed a button were excluded from further analysis.

In theory, when compared with gap detection, noise detection requires less attentional devotion to the ongoing auditory sequences. In the visual and tactile tasks, participants were instructed to pay attention to a non-auditory modality.

The auditory stimuli were delivered through Sennheiser HD 800 headphones via a Roland QUAD-CAPTURE sound card (Roland Corporation). The monitor was 23.8-inch monitor (Dell U2414H) with a frame rate of 60 Hz and resolution of 1920 x 1080 pixels. The vibration stimuli were presented by a vibrotransducer (Vp2, Acouve Laboratories) through a Roland QUAD-CAPTURE sound card (Roland Corporation) and an ESPA-10 amplifier (Soudevice, Japan). Participants placed their left middle and index fingers on the vibrotransducer and used their right index finger to press the spacebar when a vibration was detected.

Each block lasted 20 minutes with 20 minutes' break after each block. This block length was over double the previous lengths (cf. 8–10 minutes in other experiments); this was mainly because 20 minutes was the standard block length used for pupillometry works in at the NTT laboratory (Liao et al., 2016b, 2016a).

Participant exclusion

In total 16 participants attended the present experiment. When ruling out the confounds of gaze positions and blinks across tasks, six participants were excluded due to excessive blink rates. Then, a three standard deviation gaze radius threshold (red dashed rectangle in Figure 7.5A) was calculated from the remaining 10 participants' mean gaze location in the auditory gap detection task; an additional four participants were found to have average gaze positions beyond this threshold and were thus excluded. Post-exclusion average blink rate, gaze positions and fixation heat map can be found in Figure 7.5, Figure 7.6,Figure 7.7 and Figure 7.8 for all four tasks.

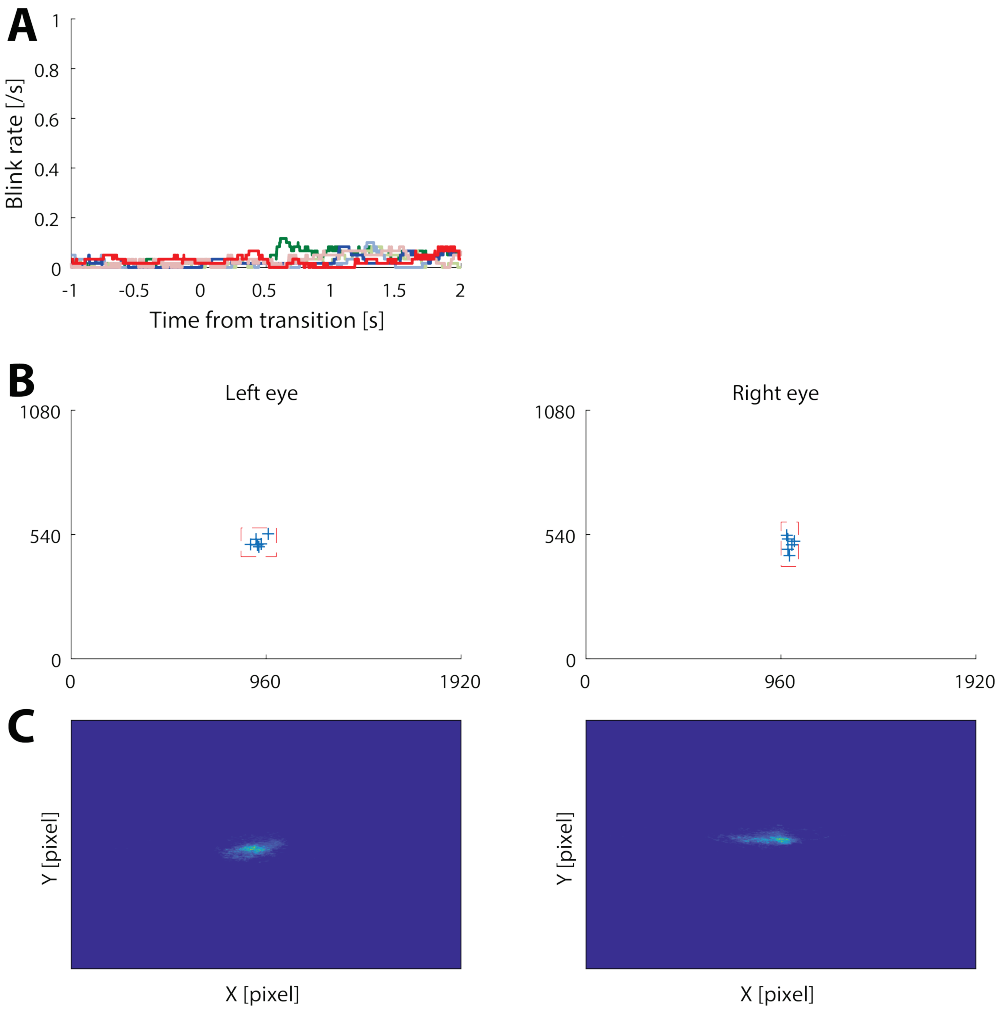


Figure 7.5 Blink and gaze locations in Experiment 7 during the auditory gap detection task (N=6). [A] Average blink rate (probability of occurrence) as a function of time relative to transition. [B] Gaze positions: The red dashed rectangle indicates the gaze radius threshold for this experiment, which is the three-standard-deviation from the mean of the gaze positions in this task. Each cross represents the average gaze position for one individual participant during this task; blue colour means this participant's average gaze position is within the threshold. [C] Heat map for gaze positions from all participants and all epochs during this task.

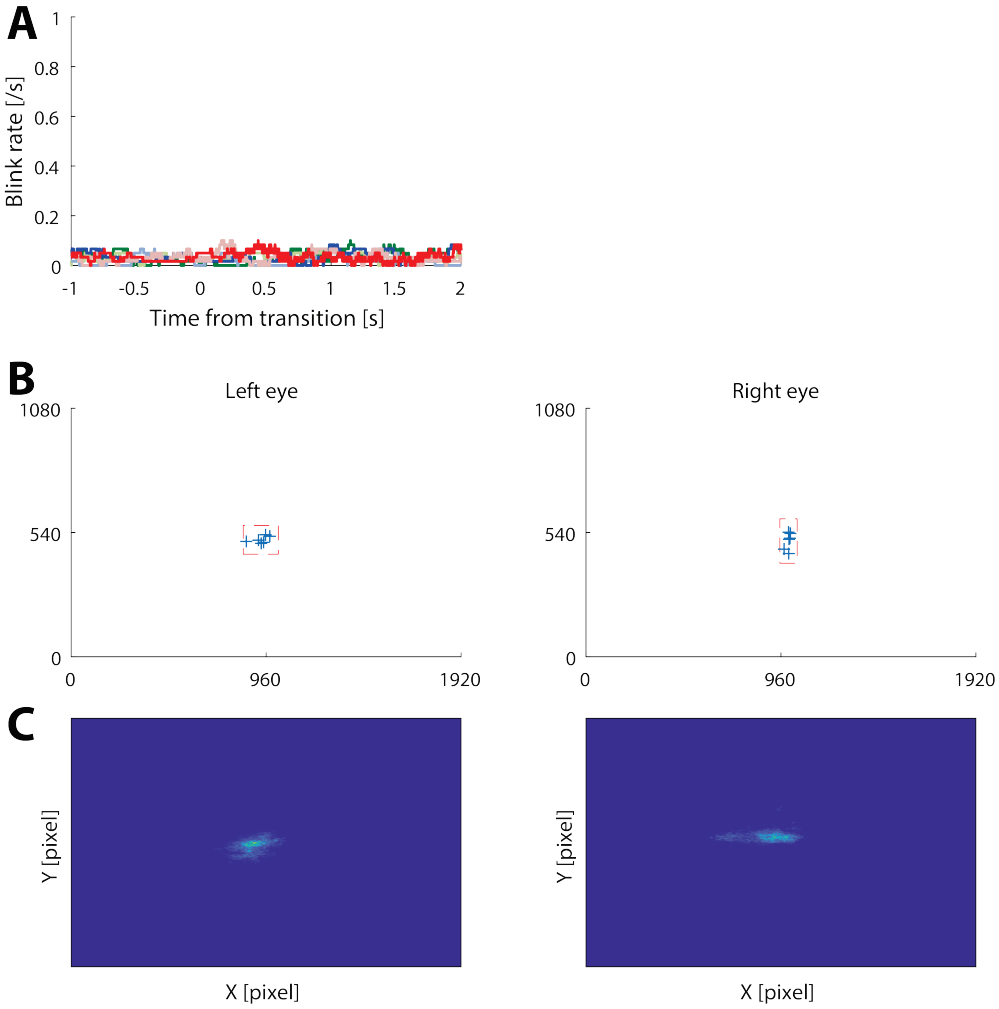


Figure 7.6 Blink and gaze locations in Experiment 7 during the visual background colour inversion task (N=6). [A] Average blink rate (probability of occurrence) as a function of time relative to transition. [B] Gaze positions: The red dashed rectangle indicates the gaze radius threshold for this experiment, which is the three-standard-deviation from the mean of the gaze positions in the auditory gap detection task in this experiment (Figure 7.5B). Each cross represents the average gaze position for one individual participant during this task; blue colour means this participant's average gaze position is within the threshold. [C] Heat map for gaze positions from all participants and all epochs during this task.

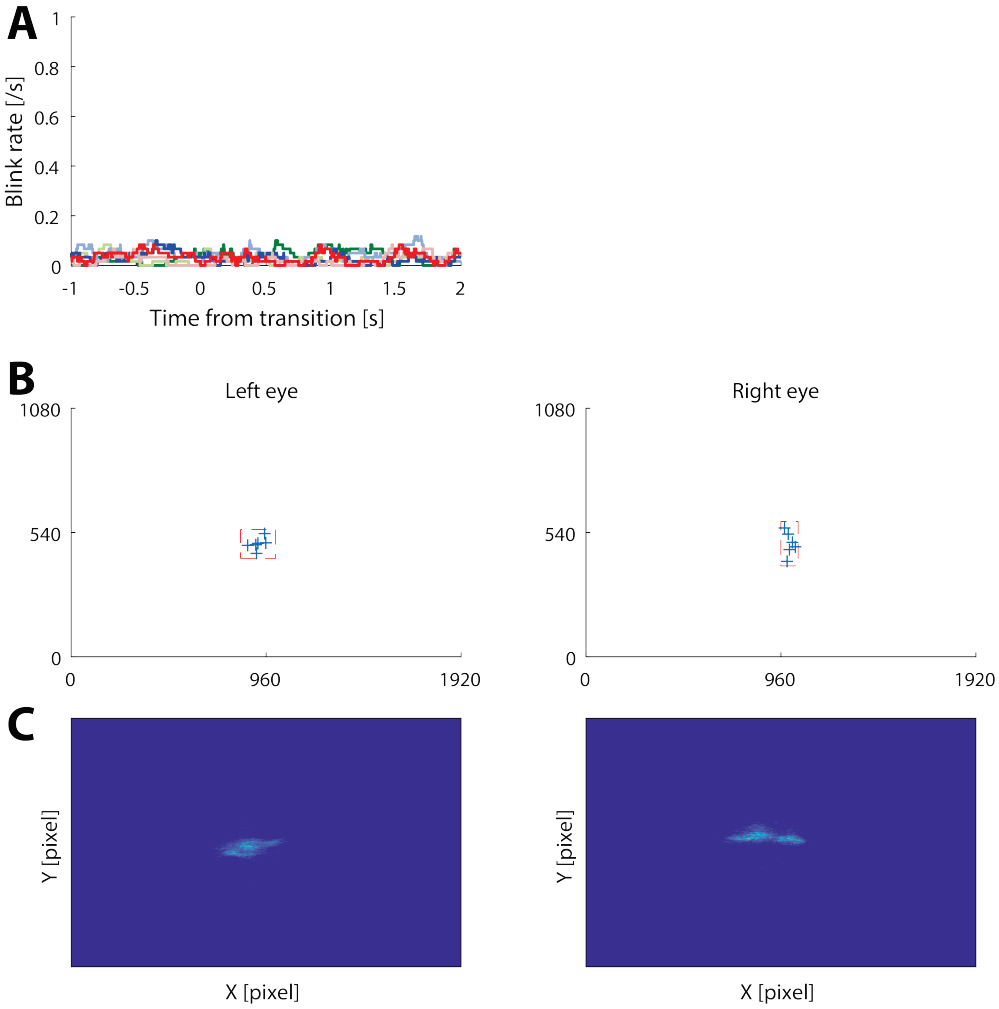


Figure 7.7 Blink and gaze locations in Experiment 7 during the auditory noise detection task (N=6). [A] Average blink rate (probability of occurrence) as a function of time relative to transition. [B] Gaze positions: The red dashed rectangle indicates the gaze radius threshold for this experiment, which is the three-standard-deviation from the mean of the gaze positions in the auditory gap detection task in this experiment (Figure 7.5B). Each cross represents the average gaze position for one individual participant during this task; blue colour means this participant's average gaze position is within the threshold. [C] Heat map for gaze positions from all participants and all epochs during this task.

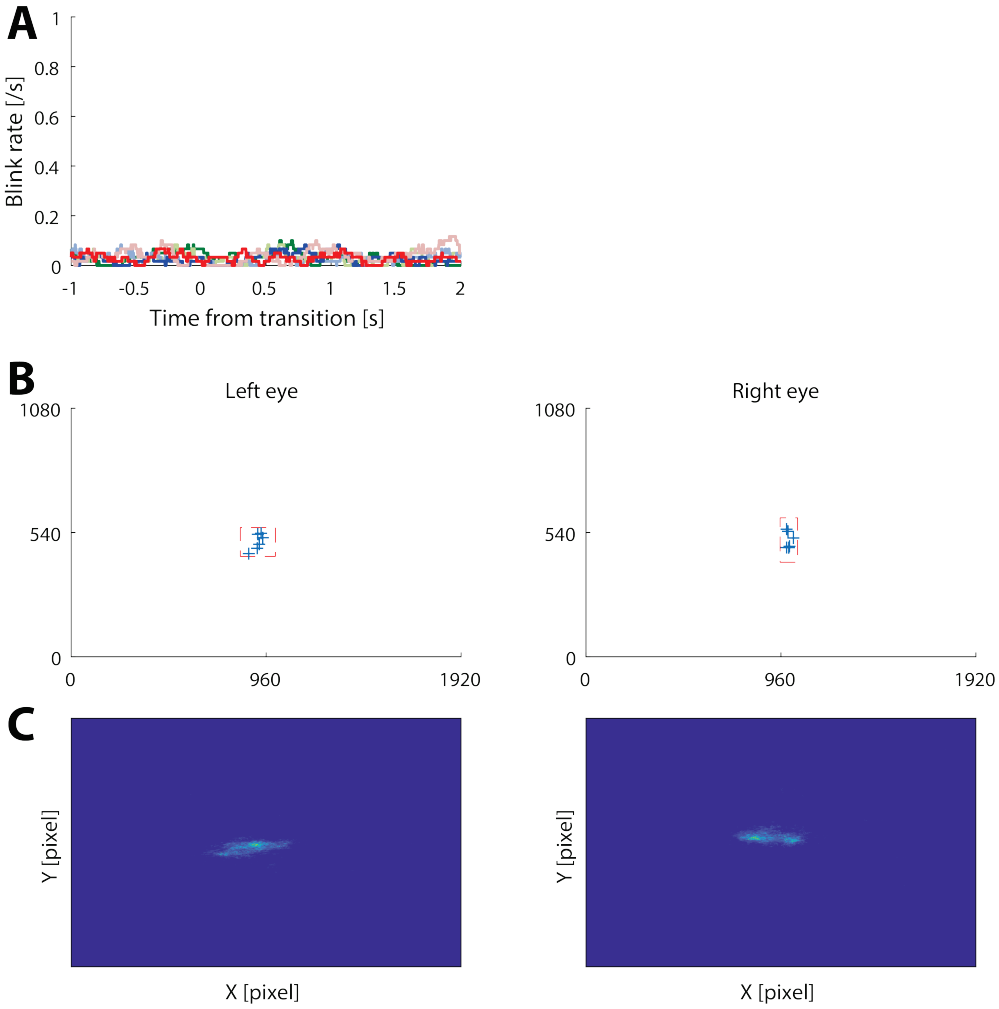


Figure 7.8 Blink and gaze locations in Experiment 7 during the tactile vibration detection task (N=6). [A] Average blink rate (probability of occurrence) as a function of time relative to transition. [B] Gaze positions: The red dashed rectangle indicates the gaze radius threshold for this experiment, which is the three-standard-deviation from the mean of the gaze positions in the auditory gap detection task in this experiment (Figure 7.5B). Each cross represents the average gaze position for one individual participant during this task; blue colour means this participant's average gaze position is within the threshold. [C] Heat map for gaze positions from all participants and all epochs during this task.

7.3.3 Results

Behavioural results

The hit rate and false alarm rate for all three transition conditions during four different tasks are presented in Table 7.2. Due to the very small sample size (N=6) and strong ceiling effect (no mistakes were made in some tasks), ANOVA analysis cannot be performed. Nevertheless, the generally high average hit rates and low false alarm rates in Table 7.2 suggest that participants performed very well in all four tasks.

	Hit Rate [%]			False Alarm Rate [%]		
	CONST	REG	RAND	CONST	REG	RAND
Auditory gap detection	100±0	83.3±10.5	75.0±11.2	0±0	3.3±3.3	5.0±5
Visual background colour inversion	100±0	100±0	100±0	0±0	0±0	0±0
Auditory noise detection	100±0	100±0	100±0	0±0	0±0	0±0
Tactile vibration detection	100±0	91.7±8.3	83.3±16.7	1.7±1.7	0±0	0±0

Table 7.2. Behavioural result (hit rate and false alarm rates) for all four tasks in Experiment 7 (N=6). Error are 1 SEM.

Average pupil diameter from stimulus transition

Figure 7.9 presents the pupil dilation response for each of the four tasks. Despite the small number of participants, the results replicate the observations of Experiment 6: the effect of pupil dilation response in the auditory gap detection task remains robust for both STEP and REG-RAND (Figure 7.9A) and disappears in the visual background colour inversion task (Figure 7.9B).

The auditory gap detection task (Figure 7.9A) confirms the same pupil dilation response pattern featured in all previous experiments of this study. Both STEP and REG-RAND evoke pupil dilation responses, showing significant divergence of pupil diameters from their respective controls post-transition, with timing patterns which match those of Experiment 1A: STEP showed a significant increase from its baseline (i.e. the response to CONST) between 700–2000ms, and REG-RAND between 920–1640ms; STEP peaks at 1420ms, and REG-RAND at 1580ms. Again, there are no observable significant differences between RAND-REG and RAND throughout the epoch. In a pattern similar to that of Experiment 1A, there is a

significant difference between REG-RAND and RAND-REG from 660ms onwards. After the transition, there is what appears to be a period where the average pupil diameter of REG-RAND is greater than that of STEP, but this is not significant throughout the epoch, and as such, this effect may be attributed to noise due to the low participant count.

Intriguingly, these pupil dilation response patterns are completely absent from the remaining three tasks: no significant pupil dilation can be discerned in any conditions of these three tasks, including the two newly introduced tasks, auditory noise burst (Figure 7.9C) and tactile vibration detection (Figure 7.9D).

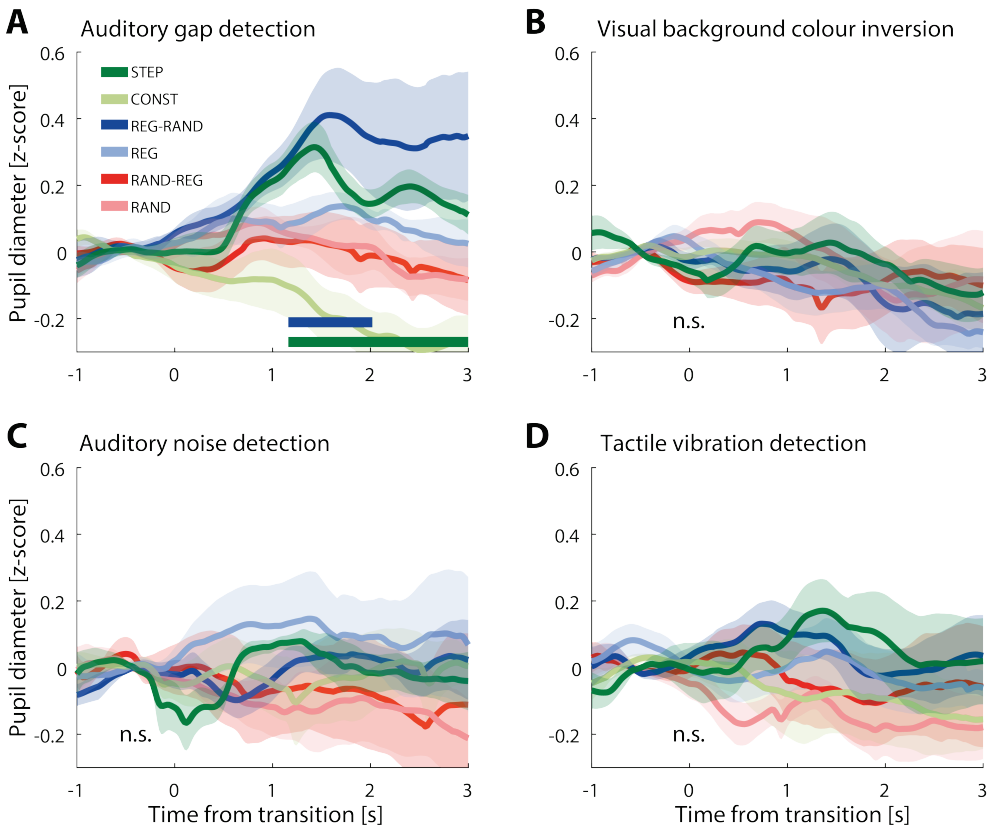


Figure 7.9 Average pupil diameter results for Experiment 7. Average pupil diameter responses to all three transitions (STEP, REG-RAND and RAND-REG) and their corresponding controls (CONST, REG, and RAND) are plotted for all four tasks, the auditory gap detection [A], the visual background colour inversion [B], the auditory noise detection [C] and the tactile vibration detection [D]. The shaded area around the solid lines shows ±1 SEM. Coloured horizontal bars below the plots indicate time intervals where cluster-level statistics show significant differences between each change condition and its no change control ($p<0.05$), using the same colour scheme as for their corresponding curves.

Pooling data from Experiment 6 and Experiment 7

Average pupil diameter

Since the auditory gap detection and visual background colour inversion tasks of Experiments 6 and 7 are identical (same task, stimuli, and trial count), data from these tasks can be pooled across both experiments to compute the pupil response (Figure 7.10). Again, there is no pupil dilation response to any condition for the pooled visual task (Figure 7.10B), further confirming the disappearance of auditory transition-based pupil responses during the visual task.

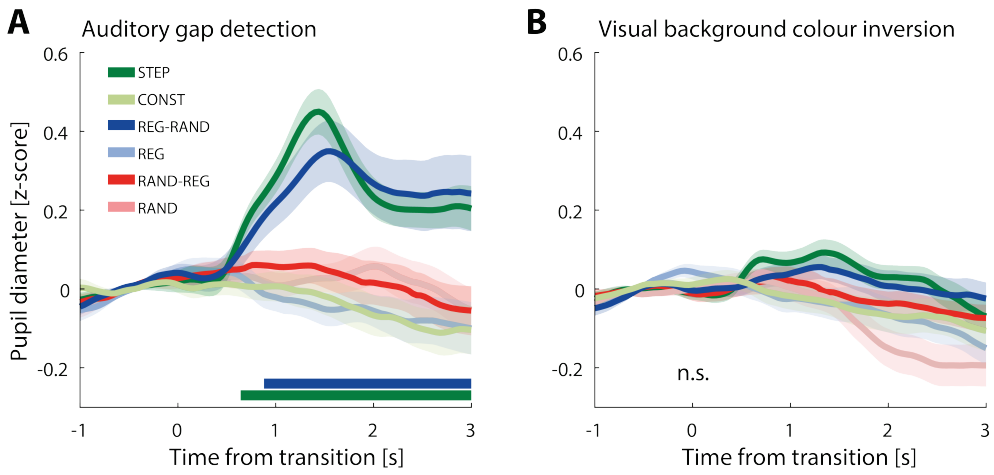


Figure 7.10 Pooled pupil diameter results from Experiments 6 and 7 (N=25) for the auditory gap detection task [A] and the visual background colour inversion task [B].

Pupil dilation rates

Pupil dilation rate analysis can be used to further examine the lack of pupil response to all stimuli in the visual background colour inversion, using pooled data from Experiments 6 and 7 as before.

The auditory gap detection task shows the same result pattern as seen in Experiment 1: An increased pupil dilation rate after the transitions STEP and REG-RAND between 0.5–1 seconds post-transition, but none for RAND-REG.

The results from the visual background colour inversion task are consistent with the null-effect of the evoked pupil responses shown previously in the average pupil diameter results (Figure 7.10), showing no significant increase in pupil dilation rate in any change

conditions with a threshold of 300ms; applying a threshold of 75ms reveals a significant, albeit small, increase in STEP 0.5–1 seconds post-transition, suggesting that STEP during the visual task may exhibit pupil dilation to a certain degree, although fewer in number and with much less temporal consistency. Nevertheless, it is evident that pupil responses observed in the auditory gap detection task are greatly diminished when switching to the visual task.

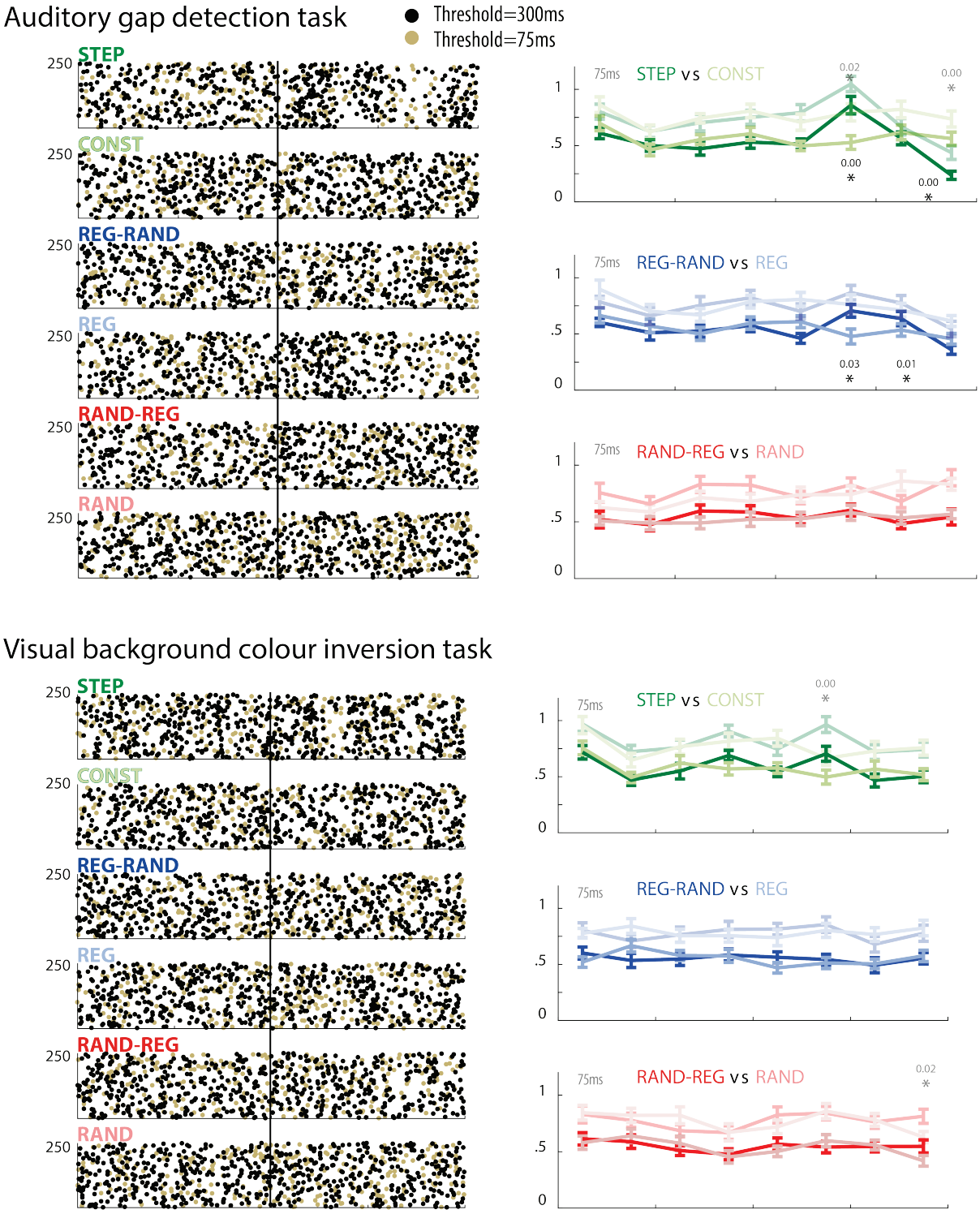


Figure 7.11 Pupil dilation rate results for two tasks: [A] the auditory gap detection task and [B] the visual background colour inversion task using data pooled from Experiments 5 and 6 (N=28). [A left] Raster plots of pupil dilation events extracted from all trials and all participants in the blocks using auditory gap detection task. Black dots represent the onset of pupil dilation events with a threshold of 300ms, and yellow-coloured dots represent the same with a shorter threshold of 75ms. The transition time is indicated with a black vertical line. [A right] The pupil dilation rate as a function of time relative to the transition (Top: STEP and CONST; Middle: REG-RAND and REG; Bottom: RAND-REG and RAND). Due to the overlapping between

the results of the two thresholds (75ms and 300ms), the pupil dilation rate with the threshold 75ms is shown in a lighter colour while the rate with threshold 300ms is shown in full colour. Asterisks, along with their p values, indicate intervals where the rates are significantly different. The results for the visual luminance task are presented in the same manner in the bottom panel.

7.4 Discussion

The series of experiments in this chapter investigates the effect of the task itself on pupil dilation responses using four different (pattern-change independent) tasks encompassing three modalities: audition, vision and touch. Based on expectations drawn from both previous research and previous chapters of this study, there was an expectation that response evocation and its characteristics would be task-independent, for example, paralleling the deviant-evoked pupil dilation responses which remain robust with or without directed attention (Liao et al., 2016b, p10; Steiner and Barry, 2011; Wetzel et al., 2016). However, contrary to these expectations, the results of this study indicated that pupil responses are completely, or at least greatly, diminished once the task does not require participants to continuously monitor the auditory stimuli, an effect observed even with frequency deviant STEP change stimuli.

This result involving the STEP transition is particularly surprising; not only is STEP a simple auditory pattern change, but also a frequency deviant. The deviant-evoked pupil dilation effect in the auditory oddball paradigm has been reported to be consistently robust even when attention is diverted towards an irrelevant visual task (Liao et al., 2016b). In this study, this null-effect in the visual task has been replicated twice, with one (Experiment 7) conducted with Liao et al. in NTT, Japan. Although the visual task in the present study and Liao et al. (2016b) differed in their auditory stimuli (rapid tone sequence vs slow auditory oddball) and visual task (background colour inversion detection task vs visual oddball task with low spatial frequency patch as a standard stimulus), the two experiments were conducted with participants from the same pool with the same equipment and facilities, and under the instruction of the same experimenter; this level of similarity in experimental techniques and environment greatly

reduces the possibility that the null-effect can be merely attributed to differences in participant, experimental and procedural factors.

The visual task in the present study reveals one particularly interesting discovery: A small, but significant increase in the pupil dilation rate to STEP is apparent despite the lack of pupil dilation in the average normalised pupil diameter – regardless of the use of pooled or unpooled data – which suggests that the pupil did indeed react to the change in STEP, but with a significantly smaller amplitude that may have been degraded by averaging and thus fails to pass statistical tests. This also implies that the average normalised pupil diameter analysis is far from exhaustive; additional analysis techniques such as pupil dilation rate should be employed in the future and even applied to past literature, possibly uncovering further enlightening findings.

Re-visiting the pupil data from the previous studies (Liao et al., 2016b; Wetzel et al., 2016), the fact that the STEP-related response was comparatively weak under the entirely passive listening condition should be unsurprising; although sufficient to evoke a pupil dilation response during passive listening tasks, general pupil responses to pure tone frequency-deviant oddballs are very weak compared to those elicited by pink noise and natural environmental sounds (Figure 7.1A). Hence, one possible explanation is that the absolute differences between the two frequencies in STEP stimuli (ranging from 28 to 1778Hz) were insufficient to evoke robust pupil responses. In consideration of this possibility, a further question naturally arises: How large must the difference be to elicit a stable and robust pupil dilation? A comparison of the differences in this study's stimuli and those of others could contribute to this finding; for example, this study uses a much faster stimulation rate (20Hz) than the simple oddball paradigm (0.3 Hz) in Liao et al. (2016b), perhaps highlighting that the sensitivity of the LC-NE system is dampened to changes in rapid stimulation especially when the attention is not focused on the stimuli.

7.4.1 Possible reasons

The effect of the deviant-evoked pupil dilation response is well-established to be task-independent by multiple independent studies (Liao et al., 2016b; Steiner and Barry, 2011; Wetzel et al., 2016), remaining robust even when attention is focused away from the auditory modality (Liao et al., 2016b). However, this study did not replicate this effect even with a simple salient frequency switch in a sequence of repeated pure tones, suggesting that the relationship between deviant-evoked pupil dilation responses and the task at hand is more convoluted than the previously considered.

In fact, this complexity was implied in Liao et al. 2016b; although the frequency deviant oddball did indeed evoke a robust pupil dilation during the visual spatial frequency change detection task (Figure 7.1C), it did not evoke any observable pupil dilation when participants were listening passively (Figure 7.1B). This result cannot be satisfactorily explained by the effect of attention, otherwise the pupil dilation response effect should be correspondingly weaker when attention is deliberately directed away from the stimuli. One possibility is that this effect is associated with general alertness during the experimental session. When not involved in any task, mind-wondering often occurs, representing a decrease in general alertness levels, in turn depressing alertness to changes in their surroundings and diminishing the sensitivity of phasic NE activity to deviants. Therefore, the visual task of the present study may be too simple and tedious to maintain the alertness of the participants. Some cues can be found amongst the behavioural results: a main effect of task on the hit rate could be interpreted as a lower performance in the auditory gap detection task. This performance disparity may reflect differences in task difficulty: Even though the same stimuli were used in all tasks, and thus resulting in the same prediction error magnitudes, the gap detection task may be slightly more challenging – something participants may possess some degree of awareness towards – making the listeners more alert overall. This increased arousal may in turn induce a general amplification of neural activity, resulting in a stronger signal of prediction error in this task, triggering phasic LC activity and thus pupil dilation. This hypothesis can be tested by examining

whether the presence of a pupil dilation response to STEP (and even REG-RAND) holds when the gap detection task is patently trivial, for example with a long gap length of over one second.

It is important to note that the gap detection task used here is identical to that of Experiment 1A, where disparities in task difficulty exist across conditions. This is because the present experiment precedes Experiment 1B chronologically, after which task difficulty and thus performance was controlled. Nevertheless, this shortcoming does not affect the results at all – as substantiated by the results of Experiment 1B. In future experiments, this is a candidate for improvement.

7.4.2 Effect of attention?

Another possible explanation is associated with attention. Although all four tasks are deliberately simple to redirect attention while occupying minimal attentional resources, they differ in where and how this attention is focused. In the auditory gap detection, in order to detect the absence of expected tones in the rapid sequences, participants need to attend closely to the auditory modality and continuously monitor the sequence. In the auditory noise burst detection task, although attention is also focused on audition, continuous monitoring is not paramount. Finally, in the visual luminance and tactile vibration tasks, attention was directed away from audition to other modalities.

The effect of attention on the pupil dilation response might not be specific to changes in complex sequence patterns but more generally associated with the sensitivity of pupil dilation responses to changes in the ongoing environment; this sensitivity may be strongly modulated by attention: the pupil dilation response might only reflect changes in the sensory input to which the beholder is attending. Unfortunately, due to equipment limitations in the present experiment, the baseline pupil diameter cannot be compared across tasks, because the Eyelink eye-tracker calibration procedure at the beginning of each task block assigns a

random arbitrary value as an initial value which cannot be compared across blocks[2]. Thus, it is not possible to conclude whether the difference in the pupil dilation effects can be attributed to attentional changes or distraction. This should be handled more carefully in future works.

7.4.3 What does this imply?

The results have shown that the change-evoked pupil response is clearly very sensitive to the task. Although phasic NE activity as an interrupt signal does not require the active detection of the unexpected changes (as seen in the auditory gap detection task), it can only be consistently observed when the participant is continuously monitoring the sequences. This implies that the LC-NE system operates automatically to report unexpected changes amongst rapidly changing sensory information, but this only applies to changes in the sensory information that the brain is continuously tracking.

In the first place, this is counterintuitive, as to keep internal representations updated and relevant, any unexpected changes in the surrounding environment must be tracked and reported to the rest of the brain for further processing – a task critical for identifying threats to survival. However, when considering the influential consequences of interrupt signals, it is understandable that the impact of a prediction error might differ when the brain is focusing on different aspects of the external environment. According to a well-known Chinese saying, “There are a thousand Hamlets in a thousand peoples’ eyes”: one text has many interpretations. Likewise, given the same sensory scene, the resulting reconstructed internal model may differ wildly depending on the observers’ foci. Hence, it can be reasonably suspected that the process of unexpected uncertainty in the LC-NE system may also act as a dynamic parametric filter controlling the changes which are allowed to pass through and trigger a reset signal, thus avoiding over-sensitivity and over-reaction to the myriad changes across

[2] See Chapter 2 ‘Normalisation’ for details.

modalities in the surrounding dynamic world. This is in accord with the proposal that the LC-NE system is a key stakeholder in the optimisation of behaviour in the Adaptive Gain Theory (Aston-Jones and Cohen, 2005).

Nevertheless, there are still many unanswered questions surrounding the effect of the tasks: What task factors – for example, the attention devoted to the transitions and the task difficulty – is the LC-NE system sensitive to? How do these factors affect NE's role? Also, does the effect of the task vary with the change itself (for example, the STEP transition of this study versus the oddball paradigm used in e.g., Liao et al., 2016b)? Clearly, the results of this chapter raise more questions than answers. More importantly, since even pupil dilation responses to the most simplistic STEP transition is affected, these questions are not limited to the role of the LC-NE system in tracking statistics in the rapid complex sound sequences, but should extend more generally to the sensitivity of the non-luminance related pupillary responses to changes in the sensory input. Therefore, it is reasonable to begin further investigations of these questions without the use of the rapid complex sequences, and STEP and CONST are suitable contenders, along with altering the construction of the tone sequences, such as tone duration, inter-tone interval and even frequency difference in STEP.

Critically, the data from this chapter has demonstrated a very important notion for researchers who are interested in pupillometry: While measuring pupil responses, the specific choice of the task that the participant performs has a major effect on the observed pupil response. This should be carefully considered when designing pupillometric experiments and interpreting data about cognition-related pupil responses.

8 General Discussion

8.1 The role of the LC-NE system in tracking rapid sensory statistics

This series of human pupillometry experiments has consistently shown robust LC-NE system responses to sudden changes in the form of pattern violations characterised as phasic NE activity, and indexed as transient pupil dilations. This finding is in line with the proposed role of the LC-NE system in arousal and attention orienting (see Sara and Bouret, 2012 for a recent review); specifically, when facing unstable environments, phasic NE responses signal unexpected uncertainty (a form of surprise) and convey interrupt signals to the rest of the brain to ensure the maintenance of accurate internal representations about the external world (Bouret and Sara, 2005; Dayan and Yu, 2006).

The present study extends our understanding of NE's role in two aspects: Firstly, contrary to previous reports, the role of NE is not restricted to behaviour-relevant contexts in which participants actively track and report changes in signals; NE has a role in coding for unexpected uncertainty even when participants are merely observing without active engagement in any change-relevant judgement. This could be considered the first observation of behaviour-free NE phasic activity in response to the types of complex pattern changes featured in the present study. Secondly, due to the rapid stimulation rate, the positive result here demonstrates that noradrenergic release is implicated in unexpected uncertainty on very rapid timescales, placing the structural content far beyond the capability of human listeners to actively track (Warren and Ackroff, 1976; Warren et al., 1991; Warren, 2008; Warren and

Obusek, 1972). As many aspects of the environment change rapidly, this provides is a basis for the signalling processes of unexpected uncertainty to operate over fast timescales to provide a reliable basis for perception.

The finding that the LC-NE system tracks changes in the sensory statistics is also congruous with theories that a primary function of our brain may be dependent on continuously predicting future events based on preceding signals drawn from the surrounding environment (Bar, 2009; Friston, 2005; Gregory, 1980; Helmholtz, 1867; Neisser, 1967; Rao and Ballard, 1999). Upon this, the present study highlights that subcortical regions also play a critical role in this process by modulating phasic LC neural activity and controlling the generation of the neuromodulator NE to signal unexpected mismatches between top-down predictions and bottom-up ongoing sensory signals.

This is also in line with the LC-NE system's role in coordinating the "fight or flight" response; unexpected uncertainty indicates that a stable and reliable aspect of the environment has changed in a potentially crucial manner, leading to the evocation of rapid physiological responses associated with physical preparedness for action. The emergence of a pattern, on the other hand, may necessitate closer cortical monitoring of the relevant source, as reflected by the MEG recordings by Barascud et al. (2016) but does not appear to be an autonomic response that is associated with NE release.

8.1.1 Disconnect between cortical and pupil dynamics

The MEG study of Barascud et al. (2016), while using the same stimuli as the present study, found strong brain responses for both the emergence and violation of patterns in naïve passive listeners. However, the present study shows that pupil responses are only sensitive to the violation of regularity, and not the emergence of regularity. This suggests that the state change observed in MEG – hypothesized to reflect rapid, bottom-up driven response modulation concomitant with adaptive predictive precision – is monitored cortically but not conveyed to the subcortical LC-NE system.

Moreover, the MEG results show MMN in the cortical response to REG-RAND but not to RAND-REG; this relationship between the responses and transition types is analogous to the relationships for evoked pupil responses. This suggests that the initiation of the phasic NE response as an interrupt signal may be associated with the cortical response to unexpected changes, namely the MMN response. One possibility is that the unexpected external change is first detected by the cortical part of the network, observed as the MMN component of the ERP, before being processed by the subcortical network involving the LC-NE system, and then activates the phasic NE response to initiate an interrupt signal to the rest of the neocortex, particularly the frontal cortex, calling for high level cognitive functions.

Note that the brain responses observed in the previous MEG study (Barascud et al., 2016) are from participants distracted away from the auditory stimuli by an incidental visual task. Similarly, Chapter 7 also employed a visual task with participants pressing a button when the screen's background switches colour. Although both experiments featured visual tasks, the cortical response showed automatic change detection while pupillometry clearly did not indicate any detection – not even during STEP, arguably the most salient and obvious change – suggesting that when the brain was distracted, changes were not delivered to the LC-NE system, although they remain cortically monitored.

This dissociation between the measures of MEG/EEG and pupillometry indicates a stark disconnect between cortical and pupil dynamics, and possibly provides new insight into how the brain processes statistics in sensory input and how the cortical and subcortical regions cooperate in this process; this provides much inspiration for future investigation.

8.1.2 Behaviour mediates responses to unexpected uncertainty

Importantly, behaviour has an influential and sophisticated effect upon pupil responses to pattern changes (see Chapter 6). While the emergence of regularity does not evoke any pupil responses when passively tracking, it does, however, elicit strong pupil responses when listeners actively seek for it. However, the significant differences in pupil responses between

passive and active conditions cannot be solely explained by motor response effects, suggesting the presence of complex interactions between automatic pupil responses associated with unexpected uncertainty and behaviour.

One way of interpreting this appearance of pupil responses to the emergence of regularity is that behaviour can mediate whether a sensory signal should be considered alike an unexpected uncertainty. Here, the brain learns the significance of the emergence and the subcortical network marks it as an unexpected uncertainty. Once this has been recognised as a regular pattern following a random pattern, the LC-NE system would then send a message to the reset of the brain indicating the importance of this change.

8.2 Is regularity salient?

Alternatively, this could also be interpreted as a modulation of the 'salience' of this transition as a result of adaption to the behavioural task. According to Itti et al. (1998), stimuli which can automatically capture attention without deliberate direction can be described as salient. In nature, the sensory signals that fall in this category – faces (Langton et al., 2008), baby cries (Formby, 1967), screams (Arnal et al., 2015), or our own names (Moray, 1959) amongst others – are interpreted as possessing a learned or genetically coded salience linked with their critical value to survival.

A wealth of evidence links the LC-NE system with attention, especially the alerting system (Beane and Marrocco, 2004; Marrocco and Davidson, 1998; see review Petersen and Posner, 2012). As a reliable indicator of phasic LC activity, the pupil dilation responses have been suggested to reflect the process of automatic attentional capture (Liao et al., 2016a; Netser et al., 2010; Wang et al., 2012, 2014; Wang and Munoz, 2014). For instance, neural activity in the superior colliculus was found to evoke a pupil dilation response to salient audiovisual stimuli (Netser et al., 2010; Wang et al., 2012, 2014). Wang et al. (Wang et al., 2014; Wang and Munoz, 2014) further found that salient audiovisual stimuli which evoke pupil

dilation response are characterised by contrast differences in visual stimuli and intensity differences in auditory stimuli. More recently, using natural sounds (e.g. laughter, scratching, crying etc.), Liao et al. (2016) also observed a correlation between the perceived loudness of the sound and the amplitude of the evoked pupil dilation.

Based on the above, the presence of pupil dilation responses might imply that the random-to-regular transition became salient to listeners when they were actively looking for it. Just as our names become salient to us once we learn their importance, the emerged regular patterns become salient under the influence of behaviour.

In this context, pupil responses to the emergence of the regularity in the absence of behavioural effects can also be interpreted as an indicator of whether regular signals can also automatically capture attention. An emerging hypothesis suggests that regular and predictable sensory patterns should be perceptually prioritised to focus limited attentional resources on stable features of the environment (Kok et al., 2012a, 2012b; Summerfield and de Lange, 2014; Summerfield and Egner, 2016; Zhao et al., 2013). This hypothesis thus conveys a fundamental consequence: regular signals should capture attention (Heilbron and Chait, 2017). Recently, the prioritisation of regularity has also been reported in the visual mortality (Zhao et al., 2013) suggesting that attention is automatically biased towards sequential regularities, even when those are irrelevant to the primary task.

Although any stimulus can become salient via association (e.g. one's name, or one's cell phone ringtone; Stothart et al., 2015), salience is known to also depend on basic properties, such as brightness or loudness, certain spectro-temporal structures and, perhaps most importantly, context and novelty (Itti and Koch, 2001; Kayser et al., 2005; Simons and Rensink, 2005). Signals that deviate from an established spatial or temporal context, such as abrupt onsets (Constantino et al., 2012; Yantis and Jonides, 1984) or other feature deviants (Itti and Baldi, 2009; Johnston et al., 1990; Kaya and Elhilali, 2017; Pearce and Hall, 1980) are hypothesized to automatically attract attention because they indicate an unexpected, and thus potentially crucial, change in the statistics of the environment.

The parameters that determine the salience of a temporal pattern itself are important to consider in this regard. For example, Turk-Browne et al. (2008) showed that repetition in visual stimuli draws infants' attention until learnt. Recent visual work (Zhao et al., 2013) has revealed that attention is biased, or say guided, to automatically learned (temporal) sequential regularities, suggesting a new framework of attentional guidance-based regularity prioritisation. Importantly, this framework cannot be explained by stimulus-driven guidance because regularity is not the physical property of any individual given stimulus but the stability of temporal relationships between stimuli, or goal-directed guidance since such regularities can still be learned without engagement in relevant tasks. This notion that temporally regular signals might be salient appears perfectly reasonable behaviourally, especially in auditory contexts, considering the prevalence of regularity in the acoustic environment, such as periodic motor sequences like footsteps, and the significance that these sounds typically convey stable and dependable contextual cues describing the properties of the surrounding world.

This notion is also consistent with the predictive coding models of perception (Feldman and Friston, 2010; Friston, 2005; Rao, 2005), which suggest that attention might arise from increased precision of probabilistic inferences in bottom-up information streams. According to Feldman and Friston (2010), signals with regularity are more reliable, thus yield predictions with higher precision; according to predictive coding, precise sensory inputs should be up-weighted and prioritised for further processing. As reviewed in Chapter 1, this precision-weighting idea has been used to describe attention under the predictive coding framework, explaining why some stimuli are more salient than others (Feldman and Friston, 2010).

If the notion that regular signals are salient is true, then the discovery of regularity should capture attention. Based on previous work in which pupil responses have been implicated in salience coding (Liao et al., 2016a; Wang et al., 2014; Wang and Munoz, 2014), the emergence of a salient auditory pattern can be reasonably expected to evoke pupil dilation responses. However, the consistent absence of pupil dilation in the present study seems to

provide counterevidence to this prediction; thus, it seems, at least in some situations, the emergence of regularity does not capture attention.

This finding is consistent with recent behavioural work by Southwell et al. (2017), in which listeners actively monitored two regular or random sequences simultaneously and detect targets (e.g. a silent gap) embedded in one of the sequences. As in the results of previous visual work (Zhao et al., 2013), it was easier to detect targets embedded within regularly repeating streams, demonstrating that regularity facilitates behavioural performance. However, if regularity (REG) is more distracting than randomness (RAND), this should be reflected by poorer target detection performance when either one of the sequences is REG. However, the results showed the contrary, indicating that REG itself is no more salient than RAND when they are presented in direct competition.

If regular signals are indeed not salient, as Heilbron and Chait commented in their recent review, this "impl[ies] that under [predictive-coding] attention is an expression of precision-weighting, but precision-weighting does not (always) express as attention. While logically possible, this creates an awkward disconnect between neural responses and cognition and calls for a more principled approach to decide when precision-weighting is attentional or not" (Heilbron and Chait, 2017, p. 13). In other words, notwithstanding the fact that the precision-weighting based description of attention (Feldman and Friston, 2010) persuasively explains the reinforcement and gravitation towards regularities (Barascud et al., 2016; Sohoglu and Chait, 2016; Southwell et al., 2017), a fundamental explicit expectation of this theory is directly refuted by experimental results (the present study and Southwell et al. 2017): that regular signals should be highly salient. This suggests that further work would be greatly beneficial to verify and potentially reappraise the precision-weighting concept, at least in the auditory domain. Moreover, this discrepancy between these auditory results and previous visual findings (e.g. Kok et al. 2012; Zhao et al., 2013) remains unclear and unresolved, requiring further exploration of cross-modality comparisons, with particular focus on possible differences in the operating mechanism of auditory and visual attention.

8.3 Future work

The studies comprising this PhD thesis raise a few questions for future research.

8.3.1 Animal electrophysiological recording

The present study uses pupillometry to index LC-NE activity. However, as discussed in Chapter 1, pupil dilation is an indirect indicator of LC-NE activity. Thus direct neuronal recordings from the LC would be desirable to confirm the findings of this study. Despite early animal studies using simple oddball paradigms, there is a lack of comprehensive verification of LC-NE activation by unexpected changes in rapid and complex stimuli, mostly as a result of shortcomings in archetypal experimental paradigms on unexpected uncertainty which involve complex decision-making that makes the training of animals very challenging. The advantage of the present paradigm is that the task is completely dissociated from the change; this study uses a gap detection task, which should be trainable in animals.

Furthermore, the disconnect between cortical and pupillary data observed in previous MEG/EEG studies and the present study suggests a structural divergence when processing REG-RAND and RAND-REG. Thus single-neuron recording can become an efficacious complement to pupillometry and neuroimaging techniques, providing a better understanding of the neural network of the regularity encoding process.

8.3.2 Human pharmacological manipulation

Undoubtedly, direct recording in humans would be most advantageous to reveal the underlying structures and processes of unexpected change detection and to confirm the role of NE in these processes. However, the small size and problematic location of the LC in the human midbrain makes data from this type of human recording almost impossible.

An alternative technique to directly confirm the role of NE in this process exploits pharmacological manipulation. There are three families of noradrenergic receptors, α_1, α_2 and

β, each having different distributions and effects. In general, excitatory effects are mediated by the α_1, and β receptors and inhibitory effects by α_2 receptors. Inhibition of LC neuronal activity can be achieved, for example, by activating α_2 receptors with its agonist clonidine and blocking βreceptors with propranolol. As reviewed in Chapter 1, Marshall et al. (2016) observed prazosin (an inverse agonist for α_1 receptors) selectively impaired the learning of uncertainty arising from changes in the environmental context. However, the results were not statistically stable, possibly due to noise in the behavioural measurements of response times.

Marrying this pharmacological manipulation with the pupillometry and stimuli paradigm of the present study has the potential to create a greatly advantageous partnership. Firstly, this paradigm does not require participants to actively respond to changes, crucially lessening the experimental burden upon participants who may suffer the side effects of NE-affecting drugs (for example dizziness, drowsiness and other low arousal symptoms). Secondly, this paradigm is relatively easy to train and does not require an excessive number of trials, making the overall experiment short, which is particularly helpful when faced with experimental time constraints such as the effective duration of drug action. Furthermore, along with the additional benefit of unobtrusive passive measurement, pupillary measures can allow measurements of participants' reactions to stimuli on a moment-by-moment basis even without any direct responses.

8.3.3 Clinical populations

The LC-NE system has been implicated in many psychiatric and neurodegenerative disorders. For instance, LC function is heavily impacted by the pathogenesis and symptoms of neurodegenerative disorders, including Parkinson's and Alzheimer's disease (Grudzien et al., 2007; Rommelfanger and Weinshenker, 2007; Weinshenker, 2008; Zarow et al., 2008); moreover, the degeneration of the LC may, in fact, contribute to some of these conditions, as many of those diagnosed with Parkinson's disease display various LC-related neuropsychiatric manifestations, from disrupted sleep to depressive disorders (McNamara and Durso, 2006).

Importantly, the LC undergoes marked degeneration in the early stages of both Alzheimer's disease (Weinshenker, 2008) and Parkinson's disease (German et al., 1992). Thus, with consideration of the LC's role in the above, how does degeneration of the LC affect the pupil responses observed in the present study? And if the pupillary effect is indeed very sensitive to degeneration of the LC, and considering the simplicity and robustness of this paradigm, could these stimuli be leveraged to help early diagnoses of Alzheimer's and Parkinson's disease?

Recently, Autism Spectrum Disorder (ASD) has been associated with potentially abnormal activity in the LC-NE system. Some studies observe a diminished ability to distinguish repetition from novelty in adults with ASD (Ewbank et al., 2015; Gomot et al., 2011; Kleinhans et al., 2009), a finding also evident in electrophysiological studies: reduced mismatch negativity (Jeste et al., 2015) and P3 responses (Falck-Ytter and von Hofsten, 2011). Recently, using pupillometric measurements, Lawson et al. (2017) found the reduced surprise in ASD is caused by abnormal phasic NE activity when learning about uncertainty. This study used a probabilistic associative learning task (den Ouden et al., 2010), in which the probability of seeing a house or face image followed by a high or low tone varied over trials; consistent probabilities produce periods of stability with highly expected outcomes while fluctuating probabilities create volatility along with unexpected and surprising outcomes. From this, there were two main findings: Firstly, the differences in physiological responses between expected and unexpected trials were much smaller or non-existent in the participants with ASD, indicating reduced modulation of response times and error rates for unexpected outcomes, borne out by a lack of difference in phasic pupil dilation, while neurotypical individuals show significant increases to surprising outcomes. Secondly, there was a correlation between behavioural manifestations of surprise and symptom severity: the smaller the difference between unexpected and expected trials, the more severe the symptoms – a result replicated in a non-clinical group, advocating the development of tests involving the learning of uncertainties in sensory input to predict the progression of ASD. Compared to the probabilistic associative learning task of Lawson et al. (2017), the comparatively straightforward paradigm

of the present study can conduce advantages which minimise testing times and simplify instruction of the participants.

Therefore, identifying the processes that detect and communicate changes in the external environment, along with the specific role of the LC-NE system in these processes, would be invaluable for both clinical diagnosis and scientific exploration.

8.3.4 Pupil event rate analysis

This study may be the first application of pupil event rate analysis in a human pupillometry study. In the present study, a deliberately wide window was used to compute the occurrences of pupil dilations and verify if the null-effect of RAND-REG could be attributed to delays in pupil dilation onsets. However, this window can be adjusted for future works depending on the purpose of the analysis; for example, a filter from analyses of neural firing rates (Dayan and Abbott, 2001) can be applied to compute a finer pupil-dilation-rate evolution, as evidenced by similar analysis for microsaccades featuring in Rolfs et al. (2008). In fact, this has been investigated in detail through another series of experiments conducted concurrently with the experiments of this thesis.

Moreover, extracting pupil events also can provide an opportunity to investigate various pupil dynamics (including the onset, peak time, duration, amplitude and speed of dilation) on a trial-by-trial basis. This allows targeted investigation of an individual participant's variations across pupil dynamics, and possibly allow linking of the individual variation in LC-NE activation with clinical situations in future work. This thus highlights a need to comprehensively investigate pupil dynamics at a single trial level, ideally combined with direct neural recording from the LC.

Furthermore, this analysis provides opportunities to investigate different components of the pupil responses – pupil dilation and pupil constriction – separately and has potential to capture much finer changes which may be neglected by across-trial averaging methods, while playing a complementary role in the interpretation and understanding of pupillometric data.

8.3.5 Complexity and length of regular/random sequences

The experiments in Chapter 5 manipulate the complexity of the regular sequences to investigate the effect of regularity length on the pupil response to the emergence of regularity (RAND-REG), observing that only the transition from a random sequence made of 20 different frequencies to a repeating tone sequence (RAND20-REG1) evoked a robust pupil dilation, which can have ascribed to the considerable contrast between randomness and repetition. Likewise, the complexity of RAND can also be engineered to determine if these pupil dilations evoked by a violation of randomness by repetition would disappear if the complexity of the RAND portion is progressively reduced: Would a transition from a two-tone random pattern to a single repeating tone (i.e. RAND2-REG1, e.g. ABBABAABABAAAAAAAAA) evoke pupil dilation?

Another outstanding question relates to the memory processes involved in unexpected uncertainty processing. It is well-established that memory retrieval via contextual prompting is stimulated by NE-mediated interactions with various neurotransmitters and hormones in the hippocampus and amygdala (Sara, 2009); NE influence on working memory through suppression via α_1 receptors and activation via α_2 receptors (Ramos and Arnsten, 2007). This is an opportunity to investigate interactions between the sensitivity of the LC-NE system to unexpected uncertainty and the length of the time window in which the sensory information is weighted, by manipulating the length (and thus complexity) of the regularity cycle in REG-RAND. In all REG-RAND stimuli used in the present study, the regularity cycle is consistently 10 tones (500ms) long, as previous behavioural results (Barascud et al., 2016) found that when the regularity cycle stretches beyond 20, detection speed markedly lags behind an ideal observer, a consequence not unreasonably attributable to attention and memory constraints of human listeners. Then, would the robust pupil dilation evoked by REG-RAND disappear if the regular portion is extended (by increasing the number of tones and/or decreasing the stimulation rate)? If yes, where does the limit lie?

Overall, a deeper characterisation of the time-scales of regularity detection and its dependence on stimulation parameters such as probability, timing or complexity of the regular patterns is desirable to tie into the existing LC-NE literature.

8.3.6 Relation with attention

Lastly, an aspect, briefly reviewed in this study, involves the effect of attention on phasic NE activity by unexpected changes in the sensory input.

It has been long proposed that the LC-NE system fulfils a vital function in the process of reorientation and targeting of attention in response to novelties which may be behaviourally significant and thus indispensable for deciding future actions. A possible initiator of this process is phasic NE activity (Bouret and Sara, 2005; Dayan and Yu, 2006), which leads to interactions between a bilateral dorsal frontoparietal network promoting objective-driven attention, and a right hemisphere-dominant ventral frontoparietal network for reaction-driven attention (Corbetta et al., 2008). From this, during periods dominated by one type of attention, the other is suppressed to avert reorientation of the focus of attention; for instance, during objective-driven attention, the prefrontal cortex inhibits the ventral network to avoid distractions, by transmitting top-down signals that suppress tonic LC activity (Corbetta et al., 2008; Dayan and Yu, 2006).

However, as alluded to by the experimental results of Chapter 7, the relationship between attention and the LC may be more complex than initially thought: there is the distinct possibility that phasic LC activity not only affects attention, but also largely depends on the object of attention. Unfortunately, due to limitations of the present study, whether the disappearance of the pupil responses to all changes observed in Chapter 7 was truly caused by attention remains unresolved.

8.4 Summary

By using the eye as a window into the brain, this thesis presents a glimpse at how the human brain navigates through the river of information raging around us and how the brain changes accordingly. This thesis follows in the footsteps of preceding efforts to extend knowledge about the role of the noradrenergic neuromodulatory system in capturing the element of surprise hidden amongst the everchanging world. There are a plethora of exciting experimental and hypothetical questions that have been brought to light by this thesis. Although much more remains to be understood, the new paradigm introduced in this thesis might provide the means to answer these questions and extend our understanding about how the brain – especially the LC-noradrenergic system – processes unexpected contextual changes in a dynamic sensory environment.

9 References

Arnal, L.H., Flinker, A., Kleinschmidt, A., Giraud, A.-L., Poeppel, D., 2015. Human Screams Occupy a Privileged Niche in the Communication Soundscape. Curr. Biol. 25, 2051–2056. https://doi.org/10.1016/j.cub.2015.06.043

Aston-Jones, G., Cohen, J.D., 2005. An Integrative Theory of Locus Coeruleus-Norepinephrine Function: Adaptive Gain and Optimal Performance. Annu. Rev. Neurosci. 28, 403–450. https://doi.org/10.1146/annurev.neuro.28.061604.135709

Aston-Jones, G., Cohen, J.D., 2005. Adaptive gain and the role of the locus coeruleus–norepinephrine system in optimal performance. J. Comp. Neurol. 493, 99–110. https://doi.org/10.1002/cne.20723

Aston-Jones, G., Rajkowski, J., Cohen, J., 2000. Locus coeruleus and regulation of behavioral flexibility and attention, in: Progress in Brain Research, Cognition, Emotion and Autonomic Responses: The Integrative Role of the Prefrontal Cortex and Limbic Structures. Elsevier, pp. 165–182. https://doi.org/10.1016/S0079-6123(00)26013-5

Aston-Jones, G., Rajkowski, J., Kubiak, P., 1997. Conditioned responses of monkey locus coeruleus neurons anticipate acquisition of discriminative behavior in a vigilance task. Neuroscience 80, 697–715. https://doi.org/10.1016/S0306-4522(97)00060-2

Aston-Jones, G., Rajkowski, J., Kubiak, P., Akaoka, H., 1992. Acute morphine induces oscillatory discharge of noradrenergic locus coeruleus neurons in the waking monkey. Neurosci. Lett. 140, 219–224. https://doi.org/10.1016/0304-3940(92)90107-I

Aston-Jones, G., Rajkowski, J., Kubiak, P., Alexinsky, T., 1994. Locus coeruleus neurons in monkey are selectively activated by attended cues in a vigilance task. J. Neurosci. 14, 4467–4480.

Aston-Jones, G., Rajkowski, J., Kubiak, P., Valentino, R.J., Shipley, M.T., 1996. Chapter 23 Role of the locus coeruleus in emotional activation, in: Holstege, G., Bandler, R., Saper, C.B. (Eds.), Progress in Brain Research, The Emotional Motor System. Elsevier, pp. 379–402. https://doi.org/10.1016/S0079-6123(08)61877-4

Atienza, M., L. Cantero, J., Gómez, C.M., 1997. The mismatch negativity component reveals the sensory memory during REM sleep in humans. Neurosci. Lett. 237, 21–24. https://doi.org/10.1016/S0304-3940(97)00798-2

Bala, A.D.S., Takahashi, T.T., 2000. Pupillary dilation response as an indicator of auditory discrimination in the barn owl. J. Comp. Physiol. A 186, 425–434. https://doi.org/10.1007/s003590050442

Bar, M., 2009. Predictions: a universal principle in the operation of the human brain. Philos. Trans. R. Soc. Lond. B Biol. Sci. 364, 1181–1182. https://doi.org/10.1098/rstb.2008.0321

Barascud, N., Pearce, M.T., Griffiths, T.D., Friston, K.J., Chait, M., 2016. Brain responses in humans reveal ideal observer-like sensitivity to complex acoustic patterns. Proc. Natl. Acad. Sci. 201508523. https://doi.org/10.1073/pnas.1508523113

Bastos, A.M., Usrey, W.M., Adams, R.A., Mangun, G.R., Fries, P., Friston, K.J., 2012. Canonical Microcircuits for Predictive Coding. Neuron 76, 695–711. https://doi.org/10.1016/j.neuron.2012.10.038

Baxter, M.G., Chiba, A.A., 1999. Cognitive functions of the basal forebrain. Curr. Opin. Neurobiol. 9, 178–183. https://doi.org/10.1016/S0959-4388(99)80024-5

Beane, M., Marrocco, R.T., 2004. Norepinephrine and acetylcholine mediation of the components of reflexive attention: implications for attention deficit disorders. Prog. Neurobiol. 74, 167–181. https://doi.org/10.1016/j.pneurobio.2004.09.001

Bear, M.F., Singer, W., 1986. Modulation of visual cortical plasticity by acetylcholine and noradrenaline. Nature 320, 172. https://doi.org/10.1038/320172a0

Beatty, J., 1982. Task-evoked pupillary responses, processing load, and the structure of processing resources. Psychol. Bull. 91, 276–292. https://doi.org/10.1037/0033-2909.91.2.276

Beatty, J., Lucero-Wagoner, B., 2000. The Pupillary System, in: Handbook of Psychophysiology. Cambridge University Press, Cambridge, MA, USA, pp. 142–162.

Bechara, A., Damasio, A.R., Damasio, H., Anderson, S.W., 1994. Insensitivity to future consequences following damage to human prefrontal cortex. Cognition 50, 7–15. https://doi.org/10.1016/0010-0277(94)90018-3

Behrens, T.E.J., Woolrich, M.W., Walton, M.E., Rushworth, M.F.S., 2007. Learning the value of information in an uncertain world. Nat. Neurosci. 10, 1214–1221. https://doi.org/10.1038/nn1954

Bendixen, A., Denham, S.L., Gyimesi, K., Winkler, I., 2010. Regular patterns stabilize auditory streams. J. Acoust. Soc. Am. 128, 3658–3666. https://doi.org/10.1121/1.3500695

Bendixen, A., Prinz, W., Horváth, J., Trujillo-Barreto, N.J., Schröger, E., 2008. Rapid extraction of auditory feature contingencies. NeuroImage 41, 1111–1119. https://doi.org/10.1016/j.neuroimage.2008.03.040

Bendixen, A., Roeber, U., Schröger, E., 2007. Regularity Extraction and Application in Dynamic Auditory Stimulus Sequences. J. Cogn. Neurosci. 19, 1664–1677. https://doi.org/10.1162/jocn.2007.19.10.1664

Bendixen, A., SanMiguel, I., Schröger, E., 2012. Early electrophysiological indicators for predictive processing in audition: A review. Int. J. Psychophysiol., Predictive information processing in the brain: Principles, neural mechanisms and models 83, 120–131. https://doi.org/10.1016/j.ijpsycho.2011.08.003

Berridge, C.W., Waterhouse, B.D., 2003. The locus coeruleus–noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. Brain Res. Rev. 42, 33–84. https://doi.org/10.1016/S0165-0173(03)00143-7

Bitsios, E. Szabadi, C.M. Bradshaw, 1998. The effects of clonidine on the fear-inhibited light reflex. J. Psychopharmacol. (Oxf.) 12, 137–145. https://doi.org/10.1177/026988119801200204

Bitsios, P., LANGLEY, R.W., SZABADI, E., BRADSHAW, C.M., 1996. Comparison of the effects of clonidine on tyramine- and methoxamine-evoked mydriasis in man. Br. J. Clin. Pharmacol. 41, 269–275. https://doi.org/10.1046/j.1365-2125.1996.03202.x

Bouret, S., Sara, S.J., 2005. Network reset: a simplified overarching theory of locus coeruleus noradrenaline function. Trends Neurosci. 28, 574–582. https://doi.org/10.1016/j.tins.2005.09.002

Bouret, S., Sara, S.J., 2004. Reward expectation, orientation of attention and locus coeruleus-medial frontal cortex interplay during learning. Eur. J. Neurosci. 20, 791–802. https://doi.org/10.1111/j.1460-9568.2004.03526.x

Bowman, E.M., Brown, V.J., Kertzman, C., Schwarz, U., Robinson, D.L., 1993. Covert orienting of attention in macaques. I. Effects of behavioral context. J. Neurophysiol. 70, 431–443. https://doi.org/10.1152/jn.1993.70.1.431

Bradley, M.M., Miccoli, L., Escrig, M.A., Lang, P.J., 2008. The pupil as a measure of emotional arousal and autonomic activation. Psychophysiology 45, 602–607. https://doi.org/10.1111/j.1469-8986.2008.00654.x

Brainard, D.H., 1997. The Psychophysics Toolbox. Spat. Vis. 10, 433–436.

Bregman, A.S., 1990. Auditory Scene Analysis: The Perceptual Organization of Sound. MIT Press.

Brisson, J., Mainville, M., Mailloux, D., Beaulieu, C., Serres, J., Sirois, S., 2013. Pupil diameter measurement errors as a function of gaze direction in corneal reflection eyetrackers. Behav. Res. Methods 45, 1322–1331. https://doi.org/10.3758/s13428-013-0327-0

Buchsbaum, B.R., Olsen, R.K., Koch, P., Berman, K.F., 2005. Human Dorsal and Ventral Auditory Streams Subserve Rehearsal-Based and Echoic Processes during Verbal Working Memory. Neuron 48, 687–697. https://doi.org/10.1016/j.neuron.2005.09.029

Bymaster, F.P., Katner, J.S., Nelson, D.L., Hemrick-Luecke, S.K., Threlkeld, P.G., Heiligenstein, J.H., Morin, S.M., Gehlert, D.R., Perry, K.W., 2002. Atomoxetine Increases Extracellular Levels of Norepinephrine and Dopamine in Prefrontal Cortex of Rat: A Potential Mechanism for Efficacy in Attention Deficit/Hyperactivity Disorder. Neuropsychopharmacology 27, 699–711. https://doi.org/10.1016/S0893-133X(02)00346-9

Campbell, F.W., Gregory, A.H., 1960. Effect of Size of Pupil on Visual Acuity. Nature 187, 1121. https://doi.org/10.1038/1871121c0

Carli, M., Robbins, T.W., Evenden, J.L., Everitt, B.J., 1983. Effects of lesions to ascending noradrenergic neurones on performance of a 5-choice serial reaction task in rats; implications for theories of dorsal noradrenergic bundle function based on selective attention and arousal. Behav. Brain Res. 9, 361–380. https://doi.org/10.1016/0166-4328(83)90138-9

Chamberlain, S.R., Müller, U., Blackwell, A.D., Clark, L., Robbins, T.W., Sahakian, B.J., 2006. Neurochemical Modulation of Response Inhibition and Probabilistic Learning in Humans. Science 311, 861–863. https://doi.org/10.1126/science.1121218

Chater, N., Tenenbaum, J.B., Yuille, A., 2006. Probabilistic models of cognition: Conceptual foundations. Elsevier.

Cheng, C.-H., Hsu, W.-Y., Shih, Y.-H., Lin, H.-C., Liao, K.-K., Wu, Z.-A., Lin, Y.-Y., 2010. Differential cerebral reactivity to shortest and longer tones: Neuromagnetic and behavioral evidence. Hear. Res. 268, 260–270. https://doi.org/10.1016/j.heares.2010.06.009

Chennu, S., Noreika, V., Gueorguiev, D., Shtyrov, Y., Bekinschtein, T.A., Henson, R., 2016. Silent Expectations: Dynamic Causal Modeling of Cortical Prediction and Attention to Sounds That Weren't. J. Neurosci. 36, 8305–8316. https://doi.org/10.1523/JNEUROSCI.1125-16.2016

Chiba, A.A., Bushnell, P.J., Oshiro, W.M., Gallagher, M., 1999. Selective removal of cholinergic neurons in the basal forebrain alters cued target detection. Neuroreport 10, 3119–3123.

Clark, A., 2016. Surfing Uncertainty: Prediction, Action, and the Embodied Mind. Oxford University Press.

Clark, A., 2013. Whatever next? Predictive brains, situated agents, and the future of cognitive science. Behav. Brain Sci. 36, 181–204. https://doi.org/10.1017/S0140525X12000477

Clifford, J.M., Day, M.D., Orwin, J.M., 1982. Reversal of clonidine induced miosis by the alpha 2-adrenoreceptor antagonist RX 781094. Br. J. Clin. Pharmacol. 14, 99–101.

Constantino, F.C., Pinggera, L., Paranamana, S., Kashino, M., Chait, M., 2012. Detection of Appearing and Disappearing Objects in Complex Acoustic Scenes. PLOS ONE 7, e46167. https://doi.org/10.1371/journal.pone.0046167

Conway, C.M., Bauernschmidt, A., Huang, S.S., Pisoni, D.B., 2010. Implicit statistical learning in language processing: Word predictability is the key. Cognition 114, 356–371. https://doi.org/10.1016/j.cognition.2009.10.009

Corbetta, M., Patel, G., Shulman, G.L., 2008. The Reorienting System of the Human Brain: From Environment to Theory of Mind. Neuron 58, 306–324. https://doi.org/10.1016/j.neuron.2008.04.017

Covington, N.V., Brown-Schmidt, S., Duff, M.C., 2018. The Necessity of the Hippocampus for Statistical Learning. J. Cogn. Neurosci. 1–20. https://doi.org/10.1162/jocn_a_01228

Cowan, N., Winkler, I., Teder, W., Näätänen, R., 1993. Memory prerequisites of mismatch negativity in the auditory event-related potential (ERP). J. Exp. Psychol. Learn. Mem. Cogn. 19, 909–921. https://doi.org/10.1037/0278-7393.19.4.909

Curet, O., Dennis, T., Scatton, B., 1987. Evidence for the involvement of presynaptic alpha-2 adrenoceptors in the regulation of norepinephrine metabolism in the rat brain. J. Pharmacol. Exp. Ther. 240, 327–336.

Dayan, P., Abbott, L.F., 2001. Theoretical neuroscience. Cambridge, MA: MIT Press.

Dayan, P., Hinton, G.E., 1996. Varieties of Helmholtz Machine. Neural Netw., Four Major Hypotheses in Neuroscience 9, 1385–1403. https://doi.org/10.1016/S0893-6080(96)00009-3

Dayan, P., Hinton, G.E., Neal, R.M., Zemel, R.S., 1995. The Helmholtz Machine. Neural Comput. 7, 889–904. https://doi.org/10.1162/neco.1995.7.5.889

Dayan, P., Yu, A., 2003. Expected and unexpected uncertainty: ACh and NE in the neocortex, in: Advances in Neural Information Processing Systems. pp. 173–180.

Dayan, P., Yu, A.J., 2006. Phasic norepinephrine: A neural interrupt signal for unexpected events. Netw. Comput. Neural Syst. 17, 335–350. https://doi.org/10.1080/09548980601004024

de Gee, J.W., Knapen, T., Donner, T.H., 2014. Decision-related pupil dilation reflects upcoming choice and individual bias. Proc. Natl. Acad. Sci. 111, E618–E625. https://doi.org/10.1073/pnas.1317557111

de Vries, M.H., Barth, A.C.R., Maiworm, S., Knecht, S., Zwitserlood, P., Flöel, A., 2009. Electrical Stimulation of Broca's Area Enhances Implicit Learning of an Artificial Grammar. J. Cogn. Neurosci. 22, 2427–2436. https://doi.org/10.1162/jocn.2009.21385

den Ouden, H.E.M., Daunizeau, J., Roiser, J., Friston, K.J., Stephan, K.E., 2010. Striatal Prediction Error Modulates Cortical Coupling. J. Neurosci. 30, 3210–3219. https://doi.org/10.1523/JNEUROSCI.4458-09.2010

Denham, S.L., Winkler, I., 2017. Predictive coding in auditory perception: challenges and unresolved questions. Eur. J. Neurosci. n/a-n/a. https://doi.org/10.1111/ejn.13802

Denham, S.L., Winkler, I., 2006. The role of predictive models in the formation of auditory streams. J. Physiol. Paris 100, 154–170. https://doi.org/10.1016/j.jphysparis.2006.09.012

Devauges, V., Sara, S.J., 1990. Activation of the noradrenergic system facilitates an attentional shift in the rat. Behav. Brain Res. 39, 19–28.

Donchin, E., Ritter, W., McCallum, W., 1978. Cognitive psychophysiology: The endogenous components of the ERP. Event-Relat. Brain Potentials Man 349–411.

Downing, C.J., 1988. Expectancy and visual-spatial attention: effects on perceptual quality. J. Exp. Psychol. Hum. Percept. Perform. 14, 188–202.

Eckstein, M.K., Guerra-Carrillo, B., Miller Singley, A.T., Bunge, S.A., 2017. Beyond eye gaze: What else can eyetracking reveal about cognition and cognitive development? Dev. Cogn. Neurosci., Sensitive periods across development 25, 69–91. https://doi.org/10.1016/j.dcn.2016.11.001

Edgar, D.M., Seidel, W.F., 1997. Modafinil Induces Wakefulness Without Intensifying Motor Activity or Subsequent Rebound Hypersomnolence in the Rat. J. Pharmacol. Exp. Ther. 283, 757–769.

Efron, B., Tibshirani, R.J., 1994. An Introduction to the Bootstrap. CRC Press.

Ego-Stengel, V., Bringuier, V., Shulz, D.E., 2002. Noradrenergic modulation of functional selectivity in the cat visual cortex: an in vivo extracellular and intracellular study. Neuroscience 111, 275–289. https://doi.org/10.1016/S0306-4522(02)00011-8

Ego-Stengel, V., Shulz, D.E., Haidarliu, S., Sosnik, R., Ahissar, E., 2001. Acetylcholine-Dependent Induction and Expression of Functional Plasticity in the Barrel Cortex of the Adult Rat. J. Neurophysiol. 86, 422–437. https://doi.org/10.1152/jn.2001.86.1.422

Einhäuser, W., 2017. The Pupil as Marker of Cognitive Processes, in: Computational and Cognitive Neuroscience of Vision, Cognitive Science and Technology. Springer, Singapore, pp. 141–169. https://doi.org/10.1007/978-981-10-0213-7_7

Einhäuser, W., Koch, C., Carter, O.L., 2010. Pupil Dilation Betrays the Timing of Decisions. Front. Hum. Neurosci. 4. https://doi.org/10.3389/fnhum.2010.00018

Einhäuser, W., Stout, J., Koch, C., Carter, O., 2008. Pupil dilation reflects perceptual selection and predicts subsequent stability in perceptual rivalry. Proc. Natl. Acad. Sci. 105, 1704–1709. https://doi.org/10.1073/pnas.0707727105

Elam, M., Svensson, T.H., Thorén, P., 1986. Locus coeruleus neurons and sympathetic nerves: Activation by cutaneous sensory afferents. Brain Res. 366, 254–261. https://doi.org/10.1016/0006-8993(86)91302-8

Eldar, E., Cohen, J.D., Niv, Y., 2013. The effects of neural gain on attention and learning. Nat. Neurosci. 16, 1146–1153. https://doi.org/10.1038/nn.3428

Eldar, E., Niv, Y., Cohen, J.D., 2016. Do You See the Forest or the Tree? Neural Gain and Breadth Versus Focus in Perceptual Processing. Psychol. Sci. 27, 1632–1643. https://doi.org/10.1177/0956797616665578

Elman, J.L., 2009. On the Meaning of Words and Dinosaur Bones: Lexical Knowledge Without a Lexicon. Cogn. Sci. 33, 547–582. https://doi.org/10.1111/j.1551-6709.2009.01023.x

Escera, C., Alho, K., Winkler, I., Näätänen, R., 1998. Neural Mechanisms of Involuntary Attention to Acoustic Novelty and Change. J. Cogn. Neurosci. 10, 590–604. https://doi.org/10.1162/089892998562997

Ewbank, M.P., Rhodes, G., Hagen, V.D., H, E.A., Powell, T.E., Bright, N., Stoyanova, R.S., Baron-Cohen, S., Calder, A.J., 2015. Repetition Suppression in Ventral Visual Cortex Is Diminished as a Function of Increasing Autistic Traits. Cereb. Cortex 25, 3381–3393. https://doi.org/10.1093/cercor/bhu149

Falck-Ytter, T., von Hofsten, C., 2011. Chapter 12 - How special is social looking in ASD: A review, in: Braddick, O., Atkinson, J., Innocenti, G.M. (Eds.), Progress in Brain Research, Gene Expression to Neurobiology and Behavior: Human Brain Development and Developmental Disorders. Elsevier, pp. 209–222. https://doi.org/10.1016/B978-0-444-53884-0.00026-9

Fanciullacci, M., Pietrini, U., Fusco, B.M., Alessandri, M., Marabini, S., Sicuteri, F., 1988. Does anisocoria by clonidine reflect a central sympathetic dysfunction in cluster headache? Clin. Neuropharmacol. 11, 56–62.

Feinberg, R., Podolak, E., 1965. Latency of pupillary reflex to light stimulation and its relationship to aging, in: Behavior, Aging and The Nervous System. Springfield.

Feldman, H., Friston, K.J., 2010. Attention, Uncertainty, and Free-Energy. Front. Hum. Neurosci. 4. https://doi.org/10.3389/fnhum.2010.00215

Fiedler, S., Glöckner, A., 2012. The Dynamics of Decision Making in Risky Choice: An Eye-Tracking Analysis. Front. Psychol. 3. https://doi.org/10.3389/fpsyg.2012.00335

Fischer, C., Morlet, D., Bouchet, P., Luaute, J., Jourdan, C., Salord, F., 1999. Mismatch negativity and late auditory evoked potentials in comatose patients. Clin. Neurophysiol. 110, 1601–1610. https://doi.org/10.1016/S1388-2457(99)00131-5

Fiser, J., Aslin, R.N., 2005. Encoding Multielement Scenes: Statistical Learning of Visual Feature Hierarchies. J. Exp. Psychol. Gen. 134, 521–537. https://doi.org/10.1037/0096-3445.134.4.521

Fiser, J., Aslin, R.N., 2002a. Statistical learning of higher-order temporal structure from visual shape sequences. J. Exp. Psychol. Learn. Mem. Cogn. 28, 458–467.

Fiser, J., Aslin, R.N., 2002b. Statistical learning of new visual feature combinations by infants. Proc. Natl. Acad. Sci. 99, 15822–15826. https://doi.org/10.1073/pnas.232472899

Fiser, J., Aslin, R.N., 2001. Unsupervised statistical learning of higher-order spatial structures from visual scenes. Psychol. Sci. 12, 499–504.

Fitch, W.T., Hauser, M.D., 2004. Computational Constraints on Syntactic Processing in a Nonhuman Primate. Science 303, 377–380. https://doi.org/10.1126/science.1089401

Foote, S.L., Bloom, F.E., Aston-Jones, G., 1983. Nucleus locus ceruleus: new evidence of anatomical and physiological specificity. Physiol. Rev. 63, 844–914.

Formby, D., 1967. Maternal Recognition of Infant's Cry. Dev. Med. Child Neurol. 9, 293–298. https://doi.org/10.1111/j.1469-8749.1967.tb02271.x

Friedman, D., Hakerem, G., Sutton, S., Fleiss, J.L., 1973. Effect of stimulus uncertainty on the pupillary dilation response and the vertex evoked potential. Electroencephalogr. Clin. Neurophysiol. 34, 475–484. https://doi.org/10.1016/0013-4694(73)90065-5

Friston, K., 2010. The free-energy principle: a unified brain theory? Nat. Rev. Neurosci. 11, 127–138. https://doi.org/10.1038/nrn2787

Friston, K., 2008. Hierarchical Models in the Brain. PLOS Comput. Biol. 4, e1000211. https://doi.org/10.1371/journal.pcbi.1000211

Friston, K., 2005. A theory of cortical responses. Philos. Trans. R. Soc. B Biol. Sci. 360, 815–836. https://doi.org/10.1098/rstb.2005.1622

Friston, K., Thornton, C., Clark, A., 2012. Free-Energy Minimization and the Dark-Room Problem. Front. Psychol. 3. https://doi.org/10.3389/fpsyg.2012.00130

Garrido, M.I., Friston, K.J., Kiebel, S.J., Stephan, K.E., Baldeweg, T., Kilner, J.M., 2008. The functional anatomy of the MMN: A DCM study of the roving paradigm. NeuroImage 42, 936–944. https://doi.org/10.1016/j.neuroimage.2008.05.018

Garrido, M.I., Kilner, J.M., Stephan, K.E., Friston, K.J., 2009. The mismatch negativity: A review of underlying mechanisms. Clin. Neurophysiol. 120, 453–463. https://doi.org/10.1016/j.clinph.2008.11.029

Garrido, M.I., Sahani, M., Dolan, R.J., 2013. Outlier Responses Reflect Sensitivity to Statistical Structure in the Human Brain. PLoS Comput Biol 9, e1002999. https://doi.org/10.1371/journal.pcbi.1002999

Gazzaley, A., Nobre, A.C., 2012. Top-down modulation: Bridging selective attention and working memory. Trends Cogn. Sci. 16, 129–135. https://doi.org/10.1016/j.tics.2011.11.014

Geiser, E., Walker, K.M.M., Bendor, D., 2014. Global timing: a conceptual framework to investigate the neural basis of rhythm perception in humans and non-human species. Audit. Cogn. Neurosci. 5, 159. https://doi.org/10.3389/fpsyg.2014.00159

German, D.C., Manaye, K.F., White, C.L., Woodward, D.J., McIntire, D.D., Smith, W.K., Kalaria, R.N., Mann, D.M., 1992. Disease-specific patterns of locus coeruleus cell loss. Ann. Neurol. 32, 667–676. https://doi.org/10.1002/ana.410320510

Gil, Z., Connors, B.W., Amitai, Y., 1997. Differential Regulation of Neocortical Synapses by Neuromodulators and Activity. Neuron 19, 679–686. https://doi.org/10.1016/S0896-6273(00)80380-3

Gilzenrat, M.S., Nieuwenhuis, S., Jepma, M., Cohen, J.D., 2010. Pupil diameter tracks changes in control state predicted by the adaptive gain theory of locus coeruleus function. Cogn. Affect. Behav. Neurosci. 10, 252–269. https://doi.org/10.3758/CABN.10.2.252

Goldinger, S.D., Papesh, M.H., 2012. Pupil Dilation Reflects the Creation and Retrieval of Memories. Curr. Dir. Psychol. Sci. 21, 90–95. https://doi.org/10.1177/0963721412436811

Gomot, M., Blanc, R., Clery, H., Roux, S., Barthelemy, C., Bruneau, N., 2011. Candidate Electrophysiological Endophenotypes of Hyper-Reactivity to Change in Autism. J. Autism Dev. Disord. 41, 705–714. https://doi.org/10.1007/s10803-010-1091-y

Gregory, R.L., 1980. Perceptions as hypotheses. Phil Trans R Soc Lond B 290, 181–197. https://doi.org/10.1098/rstb.1980.0090

Greuel, J.M., Luhmann, H.J., Singer, W., 1988. Pharmacological induction of use-dependent receptive field modifications in the visual cortex. Science 242, 74–77. https://doi.org/10.1126/science.2902687

Grudzien, A., Shaw, P., Weintraub, S., Bigio, E., Mash, D.C., Mesulam, M.M., 2007. Locus coeruleus neurofibrillary degeneration in aging, mild cognitive impairment and early Alzheimer's disease. Neurobiol. Aging 28, 327–335. https://doi.org/10.1016/j.neurobiolaging.2006.02.007

Gu, Q., 2002. Neuromodulatory transmitter systems in the cortex and their role in cortical plasticity. Neuroscience 111, 815–835. https://doi.org/10.1016/S0306-4522(02)00026-X

Hakerem, G., Sutton, S., 1966. Pupillary Response at Visual Threshold. Nature 212, 485. https://doi.org/10.1038/212485a0

Hasselmo, M.E., Linster, C., Patil, M., Ma, D., Cekic, M., 1997. Noradrenergic Suppression of Synaptic Transmission May Influence Cortical Signal-to-Noise Ratio. J. Neurophysiol. 77, 3326–3339. https://doi.org/10.1152/jn.1997.77.6.3326

Hasselmo, M.E., Wyble, B.P., Wallenstein, G.V., 1996. Encoding and retrieval of episodic memories: Role of cholinergic and GABAergic modulation in the hippocampus. Hippocampus 6, 693–708. https://doi.org/10.1002/(SICI)1098-1063(1996)6:6<693::AID-HIPO12>3.0.CO;2-W

Hauser, M.D., Newport, E.L., Aslin, R.N., 2001. Segmentation of the speech stream in a non-human primate: statistical learning in cotton-top tamarins. Cognition 78, B53–B64.

Hayes, T.R., Petrov, A.A., 2016. Mapping and correcting the influence of gaze position on pupil size measurements. Behav. Res. Methods 48, 510–527. https://doi.org/10.3758/s13428-015-0588-x

Heilbron, M., Chait, M., 2017. Great expectations: Is there evidence for predictive coding in auditory cortex? Neuroscience. https://doi.org/10.1016/j.neuroscience.2017.07.061

Helmholtz, H., 1867. Treatise on Physiological Optics, in: Handbuch der physiologischen Optik. Voss, Leipzig.

Herlenius, E., Lagercrantz, H., 2001. Neurotransmitters and neuromodulators during early human development. Early Hum. Dev. 65, 21–37. https://doi.org/10.1016/S0378-3782(01)00189-X

Hermans, E.J., Marle, H.J.F. van, Ossewaarde, L., Henckens, M.J.A.G., Qin, S., Kesteren, M.T.R. van, Schoots, V.C., Cousijn, H., Rijpkema, M., Oostenveld, R., Fernández, G., 2011. Stress-Related Noradrenergic Activity Prompts Large-Scale Neural Network Reconfiguration. Science 334, 1151–1153. https://doi.org/10.1126/science.1209603

Hess, E.H., Polt, J.M., 1964. Pupil Size in Relation to Mental Activity during Simple Problem-Solving. Science 143, 1190–1192. https://doi.org/10.1126/science.143.3611.1190

Hess, E.H., Polt, J.M., 1960. Pupil Size as Related to Interest Value of Visual Stimuli. Science 132, 349–350. https://doi.org/10.1126/science.132.3423.349

Hilton, S.M., Smith, P.R., 1984. Ventral medullary neurones excited from the hypothalamic and mid-brain defence areas. J. Auton. Nerv. Syst. 11, 35–42. https://doi.org/10.1016/0165-1838(84)90006-7

Hinton, G.E., 2007a. Learning multiple layers of representation. Trends Cogn. Sci. 11, 428–434. https://doi.org/10.1016/j.tics.2007.09.004

Hinton, G.E., 2007b. To recognize shapes, first learn to generate images. Prog. Brain Res. 165, 535–547.

Hinton, G.E., Salakhutdinov, R.R., 2006. Reducing the Dimensionality of Data with Neural Networks. Science 313, 504–507. https://doi.org/10.1126/science.1127647

Hinton, G.E., Zemel, R.S., 1994. Autoencoders, minimum description length and Helmholtz free energy, in: Advances in Neural Information Processing Systems. pp. 3–10.

Hoeks, B., Levelt, W.J.M., 1993. Pupillary dilation as a measure of attention: a quantitative system analysis. Behav. Res. Methods Instrum. Comput. 25, 16–26. https://doi.org/10.3758/BF03204445

Hohwy, J., 2013. The Predictive Mind. Oxford University Press, Oxford, New York.

Holmqvist, K., Nyström, M., Andersson, R., Dewhurst, R., Jarodzka, H., Weijer, J. van de, 2011. Eye Tracking: A comprehensive guide to methods and measures. OUP Oxford.

Horváth, J., Czigler, I., Sussman, E., Winkler, I., 2001. Simultaneously active pre-attentive representations of local and global rules for sound sequences in the human brain. Cogn. Brain Res. 12, 131–144. https://doi.org/10.1016/S0926-6410(01)00038-6

Horváth, J., Czigler, I., Winkler, I., Teder-Sälejärvi, W.A., 2007. The temporal window of integration in elderly and young adults. Neurobiol. Aging 28, 964–975. https://doi.org/10.1016/j.neurobiolaging.2006.05.002

Horváth, J., Winkler, I., 2004. How the human auditory system treats repetition amongst change. Neurosci. Lett. 368, 157–161. https://doi.org/10.1016/j.neulet.2004.07.004

Hou, R.H., Freeman, C., Langley, R.W., Szabadi, E., Bradshaw, C.M., 2005. Does modafinil activate the locus coeruleus in man? Comparison of modafinil and clonidine on arousal and autonomic functions in human volunteers. Psychopharmacology (Berl.) 181, 537–549. https://doi.org/10.1007/s00213-005-0013-8

Hsieh, C.Y., Cruikshank, S.J., Metherate, R., 2000. Differential modulation of auditory thalamocortical and intracortical synaptic transmission by cholinergic agonist. Brain Res. 880, 51–64. https://doi.org/10.1016/S0006-8993(00)02766-9

Hupé, J.-M., Lamirel, C., Lorenceau, J., 2009. Pupil dynamics during bistable motion perception. J. Vis. 9, 10–10. https://doi.org/10.1167/9.7.10

Itti, L., Baldi, P., 2009. Bayesian surprise attracts human attention. Vision Res., Visual Attention: Psychophysics, electrophysiology and neuroimaging 49, 1295–1306. https://doi.org/10.1016/j.visres.2008.09.007

Itti, L., Koch, C., 2001. Feature combination strategies for saliency-based visual attention systems. J. Electron. Imaging 10, 161–169. https://doi.org/10.1117/1.1333677

Itti, L., Koch, C., Niebur, E., 1998. A model of saliency-based visual attention for rapid scene analysis. IEEE Trans. Pattern Anal. Mach. Intell. 20, 1254–1259. https://doi.org/10.1109/34.730558

Jepma, M., Nieuwenhuis, S., 2011. Pupil Diameter Predicts Changes in the Exploration–Exploitation Trade-off: Evidence for the Adaptive Gain Theory. J. Cogn. Neurosci. 23, 1587–1596. https://doi.org/10.1162/jocn.2010.21548

Jeste, S.S., Frohlich, J., Loo, S.K., 2015. Electrophysiological biomarkers of diagnosis and outcome in neurodevelopmental disorders: Curr. Opin. Neurol. 28, 110–116. https://doi.org/10.1097/WCO.0000000000000181

Johnston, W.A., Hawley, K.J., Plewe, S.H., G, M., Jann, M., 1990. Attention capture by novel stimuli. J. Exp. Psychol. Gen. 119, 397–411. https://doi.org/10.1037/0096-3445.119.4.397

Jones, B.E., Moore, R.Y., 1977. Ascending projections of the locus coeruleus in the rat. II. Autoradiographic study. Brain Res. 127, 23–53. https://doi.org/10.1016/0006-8993(77)90378-X

Joshi, S., Li, Y., Kalwani, R.M., Gold, J.I., 2016. Relationships between Pupil Diameter and Neuronal Activity in the Locus Coeruleus, Colliculi, and Cingulate Cortex. Neuron 89, 221–234. https://doi.org/10.1016/j.neuron.2015.11.028

Kahneman, D., Beatty, J., 1966. Pupil Diameter and Load on Memory. Science 154, 1583–1585. https://doi.org/10.1126/science.154.3756.1583

Kahneman, D., Beatty, J., Pollack, I., 1967. Perceptual Deficit during a Mental Task. Science 157, 218–219. https://doi.org/10.1126/science.157.3785.218

Kaya, E.M., Elhilali, M., 2017. Modelling auditory attention. Philos. Trans. R. Soc. B 372, 20160101. https://doi.org/10.1098/rstb.2016.0101

Kayser, C., Petkov, C.I., Lippert, M., Logothetis, N.K., 2005. Mechanisms for Allocating Auditory Attention: An Auditory Saliency Map. Curr. Biol. 15, 1943–1947. https://doi.org/10.1016/j.cub.2005.09.040

Kiebel, S.J., von Kriegstein, K., Daunizeau, J., Friston, K.J., 2009. Recognizing Sequences of Sequences. PLoS Comput. Biol. 5. https://doi.org/10.1371/journal.pcbi.1000464

Kilgard, M.P., Merzenich, M.M., 1998. Cortical Map Reorganization Enabled by Nucleus Basalis Activity. Science 279, 1714–1718. https://doi.org/10.1126/science.279.5357.1714

Kimura, F., Fukuda, M., Tsumoto, T., 1999. Acetylcholine suppresses the spread of excitation in the visual cortex revealed by optical recording: possible differential effect depending on the source of input. Eur. J. Neurosci. 11, 3597–3609. https://doi.org/10.1046/j.1460-9568.1999.00779.x

Kirkham, N.Z., Slemmer, J.A., Johnson, S.P., 2002. Visual statistical learning in infancy: evidence for a domain general learning mechanism. Cognition 83, B35–B42. https://doi.org/10.1016/S0010-0277(02)00004-5

Kleinhans, N.M., Johnson, L.C., Richards, T., Mahurin, R., Greenson, J., Dawson, G., Aylward, E., 2009. Reduced Neural Habituation in the Amygdala and Social Impairments in Autism Spectrum Disorders. Am. J. Psychiatry 166, 467–475. https://doi.org/10.1176/appi.ajp.2008.07101681

Klingner, J., Tversky, B., Hanrahan, P., 2011. Effects of visual and verbal presentation on cognitive load in vigilance, memory, and arithmetic tasks. Psychophysiology 48, 323–332. https://doi.org/10.1111/j.1469-8986.2010.01069.x

Kobayashi, M., Imamura, K., Sugai, T., Onoda, N., Yamamoto, M., Komai, S., Watanabe, Y., 2000. Selective suppression of horizontal propagation in rat visual cortex by norepinephrine. Eur. J. Neurosci. 12, 264–272.

Koelewijn, T., Bronkhorst, A., Theeuwes, J., 2009. Auditory and visual capture during focused visual attention. J. Exp. Psychol. Hum. Percept. Perform. 35, 1303–1315. https://doi.org/10.1037/a0013901

Koelewijn, T., de Kluiver, H., Shinn-Cunningham, B.G., Zekveld, A.A., Kramer, S.E., 2015. The pupil response reveals increased listening effort when it is difficult to focus attention. Hear. Res. 323, 81–90. https://doi.org/10.1016/j.heares.2015.02.004

Koelewijn, T., Shinn-Cunningham, B.G., Zekveld, A.A., Kramer, S.E., 2014. The pupil response is sensitive to divided attention during speech processing. Hear. Res. 312, 114–120. https://doi.org/10.1016/j.heares.2014.03.010

Koelewijn, T., Zekveld, A.A., Festen, J.M., Kramer, S.E., 2012. Pupil Dilation Uncovers Extra Listening Effort in the Presence of a Single-Talker Masker. Ear Hear. 33, 291. https://doi.org/10.1097/AUD.0b013e3182310019

Kok, P., Jehee, J.F.M., de Lange, F.P., 2012a. Less is more: expectation sharpens representations in the primary visual cortex. Neuron 75, 265–270. https://doi.org/10.1016/j.neuron.2012.04.034

Kok, P., Rahnev, D., Jehee, J.F.M., Lau, H.C., Lange, F.P. de, 2012b. Attention Reverses the Effect of Prediction in Silencing Sensory Signals. Cereb. Cortex 22, 2197–2206. https://doi.org/10.1093/cercor/bhr310

Kozicz, T., Bittencourt, J.C., May, P.J., Reiner, A., Gamlin, P.D.R., Palkovits, M., Horn, A.K.E., Toledo, C.A.B., Ryabinin, A.E., 2011. The Edinger-Westphal nucleus: A historical, structural, and functional perspective on a dichotomous terminology. J. Comp. Neurol. 519, 1413–1434. https://doi.org/10.1002/cne.22580

Krishnamurthy, K., Nassar, M.R., Sarode, S., Gold, J.I., 2017. Arousal-related adjustments of perceptual biases optimize perception in dynamic environments. Nat. Hum. Behav. 1, s41562-017-0107–017. https://doi.org/10.1038/s41562-017-0107

Laeng, B., Sirois, S., Gredebäck, G., 2012. Pupillometry: A Window to the Preconscious? Perspect. Psychol. Sci. 7, 18–27. https://doi.org/10.1177/1745691611427305

Langton, S.R.H., Law, A.S., Burton, A.M., Schweinberger, S.R., 2008. Attention capture by faces. Cognition 107, 330–342. https://doi.org/10.1016/j.cognition.2007.07.012

Lapiz, M.D.S., Bondi, C.O., Morilak, D.A., 2007. Chronic Treatment with Desipramine Improves Cognitive Performance of Rats in an Attentional Set-Shifting Test. Neuropsychopharmacology 32, 1000. https://doi.org/10.1038/sj.npp.1301235

Lapiz, M.D.S., Morilak, D.A., 2006. Noradrenergic modulation of cognitive function in rat medial prefrontal cortex as measured by attentional set shifting capability. Neuroscience 137, 1039–1049. https://doi.org/10.1016/j.neuroscience.2005.09.031

Laughlin, S.B., 1992. Retinal information capacity and the function of the pupil. Ophthalmic Physiol. Opt. 12, 161–164. https://doi.org/10.1111/j.1475-1313.1992.tb00281.x

Lavín, C., San Martín, R., Rosales Jubal, E., 2014. Pupil dilation signals uncertainty and surprise in a learning gambling task. Front. Behav. Neurosci. 7. https://doi.org/10.3389/fnbeh.2013.00218

Lawson, R.P., Mathys, C., Rees, G., 2017. Adults with autism overestimate the volatility of the sensory environment. Nat. Neurosci. advance online publication. https://doi.org/10.1038/nn.4615

Lee, T.S., Mumford, D., 2003. Hierarchical Bayesian inference in the visual cortex. JOSA A 20, 1434–1448.

Levin, B.E., Craik, R.L., Hand, P.J., 1988. The role of norepinephrine in adult rat somatosensory (SmI) cortical metabolism and plasticity. Brain Res. 443, 261–271. https://doi.org/10.1016/0006-8993(88)91620-4

Liao, H.-I., Kidani, S., Yoneya, M., Kashino, M., Furukawa, S., 2016a. Correspondences among pupillary dilation response, subjective salience of sounds, and loudness. Psychon. Bull. Rev. 23, 412–425. https://doi.org/10.3758/s13423-015-0898-0

Liao, H.-I., Yoneya, M., Kidani, S., Kashino, M., Furukawa, S., 2016b. Human Pupillary Dilation Response to Deviant Auditory Stimuli: Effects of Stimulus Properties and Voluntary Attention. Front. Neurosci., Auditory Cognitive Neuroscience 10. https://doi.org/10.3389/fnins.2016.00043

Libby, W.L., Lacey, B.C., Lacey, J.I., 1973. Pupillary and Cardiac Activity During Visual Attention. Psychophysiology 10, 270–294. https://doi.org/10.1111/j.1469-8986.1973.tb00526.x

Loewenfeld, I.E., Lowenstein, O., 1993. The Pupil: Anatomy, Physiology, and Clinical Applications. Butterworth-Heinemann.

Loewy, A.D., Wallach, J.H., McKellar, S., 1981. Efferent connections of the ventral medulla oblongata in the rat. Brain Res. Rev. 3, 63–80. https://doi.org/10.1016/0165-0173(81)90012-6

MacKay, D.J.C., 2003. Information Theory, Inference and Learning Algorithms. Cambridge University Press.

MacLachlan, C., Howland, H.C., 2002. Normal values and standard deviations for pupil diameter and interpupillary distance in subjects aged 1 month to 19 years. Ophthalmic Physiol. Opt. 22, 175–182. https://doi.org/10.1046/j.1475-1313.2002.00023.x

Madras, B.K., Xie, Z., Lin, Z., Jassen, A., Panas, H., Lynch, L., Johnson, R., Livni, E., Spencer, T.J., Bonab, A.A., Miller, G.M., Fischman, A.J., 2006. Modafinil Occupies Dopamine and Norepinephrine Transporters in Vivo and Modulates the Transporters and Trace Amine Activity in Vitro. J. Pharmacol. Exp. Ther. 319, 561–569. https://doi.org/10.1124/jpet.106.106583

Maher, T., Furedy, J., 1979. A comparison of the pupillary and electrodermal components of the orienting reflex in sensitivity of initial stimulus presentation, repetition and change, in: Kimmel, H., van Olst, E., Orlebeke, J. (Eds.), The Orienting Reflex in Humans. Lawrence Erlbaum Associates, New York, pp. 381–391.

Makuuchi, M., Bahlmann, J., Anwander, A., Friederici, A.D., 2009. Segregating the core computational faculty of human language from working memory. Proc. Natl. Acad. Sci. U. S. A. 106, 8362–8367. https://doi.org/10.1073/pnas.0810928106

Maris, E., Oostenveld, R., 2007. Nonparametric statistical testing of EEG- and MEG-data. J. Neurosci. Methods 164, 177–190. https://doi.org/10.1016/j.jneumeth.2007.03.024

Marrocco, R., Davidson, M., 1998. Neurochemistry of attention, in: Parasuraman, R. (Ed.), The Attentive Brain. The MIT Press, Cambridge, MA, pp. 35–50.

Marshall, L., Mathys, C., Ruge, D., Berker, A.O. de, Dayan, P., Stephan, K.E., Bestmann, S., 2016. Pharmacological Fingerprints of Contextual Uncertainty. PLOS Biol. 14, e1002575. https://doi.org/10.1371/journal.pbio.1002575

Mathys, C.D., Lomakina, E.I., Daunizeau, J., Iglesias, S., Brodersen, K.H., Friston, K.J., Stephan, K.E., 2014. Uncertainty in perception and the Hierarchical Gaussian Filter. Front. Hum. Neurosci. 8. https://doi.org/10.3389/fnhum.2014.00825

McClelland, J., Rumelhart, D., 1981. An Interactive Activation Model of Context Effects in Letter Perception: Part 1. An Account of Basic Findings. Psychol. Rev. 88.

McDermott, J.H., Oxenham, A.J., Simoncelli, E.P., 2009. Sound texture synthesis via filter statistics, in: IEEE Workshop on Applications of Signal Processing to Audio and Acoustics, 2009. WASPAA '09. Presented at the IEEE Workshop on Applications of Signal Processing to Audio and Acoustics, 2009. WASPAA '09, pp. 297–300. https://doi.org/10.1109/ASPAA.2009.5346467

McDermott, J.H., Schemitsch, M., Simoncelli, E.P., 2013. Summary statistics in auditory perception. Nat. Neurosci. 16, 493–498. https://doi.org/10.1038/nn.3347

McDermott, J.H., Wrobleski, D., Oxenham, A.J., 2011. Recovering sound sources from embedded repetition. Proc. Natl. Acad. Sci. 108, 1188–1193. https://doi.org/10.1073/pnas.1004765108

McDougal, D.H., Gamlin, P.D., 2015. Autonomic control of the eye. Compr. Physiol. 5, 439–473. https://doi.org/10.1002/cphy.c140014

McGaughy, J., Ross, R.S., Eichenbaum, H., 2008. Noradrenergic, but not cholinergic, deafferentation of prefrontal cortex impairs attentional set-shifting. Neuroscience 153, 63–71. https://doi.org/10.1016/j.neuroscience.2008.01.064

McGinley, M.J., Vinck, M., Reimer, J., Batista-Brito, R., Zagha, E., Cadwell, C.R., Tolias, A.S., Cardin, J.A., McCormick, D.A., 2015. Waking State: Rapid Variations Modulate Neural and Behavioral Responses. Neuron 87, 1143–1161. https://doi.org/10.1016/j.neuron.2015.09.012

McNamara, P., Durso, R., 2006. Neuropharmacological treatment of mental dysfunction in Parkinson's disease. Behav. Neurol. 17, 43–51.

Megela, A.L., Teyler, T.J., 1979. Habituation and the human evoked potential. J. Comp. Physiol. Psychol. 93, 1154–1170.

Metherate, R., Weinberger, N.M., 1990. Cholinergic modulation of responses to single tones produces tone-specific receptive field alterations in cat auditory cortex. Synapse 6, 133–145. https://doi.org/10.1002/syn.890060204

Milne, A.E., Petkov, C.I., Wilson, B., 2017. Auditory and visual sequence learning in humans and monkeys using an artificial grammar learning paradigm. Neuroscience. https://doi.org/10.1016/j.neuroscience.2017.06.059

Minzenberg, M.J., Watrous, A.J., Yoon, J.H., Ursu, S., Carter, C.S., 2008. Modafinil Shifts Human Locus Coeruleus to Low-Tonic, High-Phasic Activity During Functional MRI. Science 322, 1700–1702. https://doi.org/10.1126/science.1164908

Molholm, S., Martinez, A., Ritter, W., Javitt, D.C., Foxe, J.J., 2005. The Neural Circuitry of Pre-attentive Auditory Change-detection: An fMRI Study of Pitch and Duration Mismatch Negativity generators. Cereb. Cortex 15, 545–551. https://doi.org/10.1093/cercor/bhh155

Moore, R., Bloom, F.E., 1979. Central Catecholamine Neuron Systems: Anatomy and Physiology of the Norepinephrine and Epinephrine Systems. Annu. Rev. Neurosci. 2, 113–168. https://doi.org/10.1146/annurev.ne.02.030179.000553

Moray, N., 1959. Attention in dichotic listening: Affective cues and the influence of instructions. Q. J. Exp. Psychol. 11, 56–60. https://doi.org/10.1080/17470215908416289

Morlet, D., Fischer, C., 2013. MMN and Novelty P3 in Coma and Other Altered States of Consciousness: A Review. Brain Topogr. 27, 467–479. https://doi.org/10.1007/s10548-013-0335-5

Morley, M., Bradshaw, C., Szabadi, E., 1991. Effects of clonidine and yohimbine on the pupillary light reflex and carbachol-evoked sweating in healthy volunteers. Br. J. Clin. Pharmacol. 31, 99–101. https://doi.org/10.1111/j.1365-2125.1991.tb03864.x

Mouraux, A., Iannetti, G.D., 2008. Across-trial averaging of event-related EEG responses and beyond. Magn. Reson. Imaging, Proceedings of the International School on Magnetic Resonance and Brain Function 26, 1041–1054. https://doi.org/10.1016/j.mri.2008.01.011

Murphy, P.R., O'Connell, R.G., O'Sullivan, M., Robertson, I.H., Balsters, J.H., 2014. Pupil diameter covaries with BOLD activity in human locus coeruleus. Hum. Brain Mapp. 35, 4140–4154. https://doi.org/10.1002/hbm.22466

Murphy, P.R., Robertson, I.H., Balsters, J.H., O'connell, R.G., 2011. Pupillometry and P3 index the locus coeruleus-noradrenergic arousal function in humans. Psychophysiology 48, 1532–1543. https://doi.org/10.1111/j.1469-8986.2011.01226.x

Näätänen, R., 1992. Attention and Brain Function. Psychology Press.

Näätänen, R., Astikainen, P., Ruusuvirta, T., Huotilainen, M., 2010. Automatic auditory intelligence: An expression of the sensory–cognitive core of cognitive processes. Brain Res. Rev. 64, 123–136. https://doi.org/10.1016/j.brainresrev.2010.03.001

Näätänen, R., Gaillard, A.W.K., Mäntysalo, S., 1978. Early selective-attention effect on evoked potential reinterpreted. Acta Psychol. (Amst.) 42, 313–329. https://doi.org/10.1016/0001-6918(78)90006-9

Näätänen, R., Paavilainen, P., Rinne, T., Alho, K., 2007. The mismatch negativity (MMN) in basic research of central auditory processing: A review. Clin. Neurophysiol. 118, 2544–2590. https://doi.org/10.1016/j.clinph.2007.04.026

Näätänen, R., Paavilainen, P., Titinen, H., Jiang, D., Alho, K., 1993. Attention and mismatch negativity. Psychophysiology 30, 436–450. https://doi.org/10.1111/j.1469-8986.1993.tb02067.x

Näätänen, R., Rinne, T., 2002. Electric brain response to sound repetition in humans: an index of long-term-memory – trace formation? Neurosci. Lett. 318, 49–51. https://doi.org/10.1016/S0304-3940(01)02438-7

Näätänen, R., Winkler, I., 1999. The concept of auditory stimulus representation in cognitive neuroscience. Psychol. Bull. 125, 826–859. https://doi.org/10.1037/0033-2909.125.6.826

Naber, M., Alvarez, G.A., Nakayama, K., 2013. Tracking the allocation of attention using human pupillary oscillations. Front. Psychol. 4. https://doi.org/10.3389/fpsyg.2013.00919

Nair, V., Hinton, G.E., 2006. Inferring motor programs from images of handwritten digits, in: Advances in Neural Information Processing Systems. pp. 515–522.

Nassar, M.R., Rumsey, K.M., Wilson, R.C., Parikh, K., Heasly, B., Gold, J.I., 2012. Rational regulation of learning dynamics by pupil-linked arousal systems. Nat. Neurosci. 15, 1040–1046. https://doi.org/10.1038/nn.3130

Nassar, M.R., Wilson, R.C., Heasly, B., Gold, J.I., 2010. An Approximately Bayesian Delta-Rule Model Explains the Dynamics of Belief Updating in a Changing Environment. J. Neurosci. 30, 12366–12378. https://doi.org/10.1523/JNEUROSCI.0822-10.2010

Natan, R.G., Briguglio, J.J., Mwilambwe-Tshilobo, L., Jones, S.I., Aizenberg, M., Goldberg, E.M., Geffen, M.N., 2015. Complementary control of sensory adaptation by two types of cortical interneurons. eLife 4, e09868. https://doi.org/10.7554/eLife.09868

Neisser, U., 1967. Cognitive psychology. Appleton-Century-Crofts.

Netser, S., Ohayon, S., Gutfreund, Y., 2010. Multiple Manifestations of Microstimulation in the Optic Tectum: Eye Movements, Pupil Dilations, and Sensory Priming. J. Neurophysiol. 104, 108–118. https://doi.org/10.1152/jn.01142.2009

Newman, N.J., Miller, N.R., Biousse, V., 2008. Walsh and Hoyt's Clinical Neuro-ophthalmology: The Essentials. Lippincott Williams & Wilkins.

Nieuwenhuis, S., Aston-Jones, G., Cohen, J.D., 2005. Decision making, the P3, and the locus coeruleus--norepinephrine system. Psychol. Bull. 131, 510–532. https://doi.org/10.1037/0033-2909.131.4.510

Nieuwenhuis, S., Forstmann, B.U., Wagenmakers, E.-J., 2011. Erroneous analyses of interactions in neuroscience: a problem of significance. Nat. Neurosci. 14, 1105–1107. https://doi.org/10.1038/nn.2886

Oostenveld, R., Fries, P., Maris, E., Schoffelen, J.-M., Oostenveld, R., Fries, P., Maris, E., Schoffelen, J.-M., 2010. FieldTrip: Open Source Software for Advanced Analysis of MEG, EEG, and Invasive Electrophysiological Data, FieldTrip: Open Source Software for Advanced Analysis of MEG, EEG, and Invasive Electrophysiological Data. Comput. Intell. Neurosci. Comput. Intell. Neurosci. 2011, 2011, e156869. https://doi.org/10.1155/2011/156869, 10.1155/2011/156869

Opitz, B., Rinne, T., Mecklinger, A., von Cramon, D.Y., Schröger, E., 2002. Differential Contribution of Frontal and Temporal Cortices to Auditory Change Detection: fMRI and ERP Results. NeuroImage 15, 167–174. https://doi.org/10.1006/nimg.2001.0970

Paavilainen, P., Araj??rvi, P., Takegata, R., 2007. Preattentive detection of nonsalient contingencies between auditory features: NeuroReport 18, 159–163. https://doi.org/10.1097/WNR.0b013e328010e2ac

Panckeri, K.A., Schotland, H.M., Pack, A.I., Hendricks, J.C., 1996. Modafinil Decreases Hypersomnolence in the English Bulldog, a Natural Animal Model of Sleep-Disordered Breathing. Sleep 19, 626–631. https://doi.org/10.1093/sleep/19.8.626

Parasuraman, R., Greenwood, P.M., Haxby, J.V., Grady, C.L., 1992. VISUOSPATIAL ATTENTION IN DEMENTIA OF THE ALZHEIMER TYPE. Brain 115, 711–733. https://doi.org/10.1093/brain/115.3.711

Parnavelas, J.G., Blue, M.E., 1982. The role of the noradrenergic system on the formation of synapses in the visual cortex of the rat. Dev. Brain Res. 3, 140–144. https://doi.org/10.1016/0165-3806(82)90082-7

Payzan-LeNestour, E., Dunne, S., Bossaerts, P., O'Doherty, J.P., 2013. The Neural Representation of Unexpected Uncertainty during Value-Based Decision Making. Neuron 79, 191–201. https://doi.org/10.1016/j.neuron.2013.04.037

Pearce, J.M., Hall, G., 1980. A model for Pavlovian learning: Variations in the effectiveness of conditioned but not of unconditioned stimuli. Psychol. Rev. 87, 532–552. https://doi.org/10.1037/0033-295X.87.6.532

Pearce, M.T., 2005. The construction and evaluation of statistical models of melodic structure in music perception and composition. City University London.

Pérez-González, D., Malmierca, M.S., 2014. Adaptation in the auditory system: an overview. Front. Integr. Neurosci. 8. https://doi.org/10.3389/fnint.2014.00019

Petersen, S.E., Posner, M.I., 2012. The Attention System of the Human Brain: 20 Years After. Annu. Rev. Neurosci. 35, 73–89. https://doi.org/10.1146/annurev-neuro-062111-150525

Petersson, K.M., Forkstam, C., Ingvar, M., 2004. Artificial syntactic violations activate Broca's region. Cogn. Sci. 28, 383–407. https://doi.org/10.1016/j.cogsci.2003.12.003

Phillips, H.N., Blenkmann, A., Hughes, L.E., Bekinschtein, T.A., Rowe, J.B., 2015. Hierarchical Organization of Frontotemporal Networks for the Prediction of Stimuli across Multiple Dimensions. J. Neurosci. 35, 9255–9264. https://doi.org/10.1523/JNEUROSCI.5095-14.2015

Phillips, H.N., Blenkmann, A., Hughes, L.E., Kochen, S., Bekinschtein, T.A., CAN, C., Rowe, J.B., 2016. Convergent evidence for hierarchical prediction networks from human electrocorticography and magnetoencephalography. Cortex. https://doi.org/10.1016/j.cortex.2016.05.001

Phillips, M.A., Szabadi, E., Bradshaw, C.M., 2000. Comparison of the effects of clonidine and yohimbine on pupillary diameter at different illumination levels. Br. J. Clin. Pharmacol. 50, 65–68. https://doi.org/10.1046/j.1365-2125.2000.00225.x

Pineda, J.A., Westerfield, M., Kronenberg, B.M., Kubrin, J., 1997. Human and monkey P3-like responses in a mixed modality paradigm: effects of context and context-dependent noradrenergic influences. Int. J. Psychophysiol. 27, 223–240. https://doi.org/10.1016/S0167-8760(97)00061-5

Polich, J., 2012. Detection of Change: Event-Related Potential and fMRI Findings. Springer Science & Business Media.

Posner, M.I., Petersen, S.E., 1990. The Attention System of the Human Brain. Annu. Rev. Neurosci. 13, 25–42. https://doi.org/10.1146/annurev.ne.13.030190.000325

Preuschoff, K., 't Hart, B.M., Einhäuser, W., 2011. Pupil Dilation Signals Surprise: Evidence for Noradrenaline's Role in Decision Making. Front. Neurosci. 5. https://doi.org/10.3389/fnins.2011.00115

Privitera, C.M., Renninger, L.W., Carney, T., Klein, S., Aguilar, M., 2010. Pupil dilation during visual target detection. J. Vis. 10, 3–3. https://doi.org/10.1167/10.10.3

Qiyuan, J., Richer, F., Wagoner, B.L., Beatty, J., 1985. The Pupil and Stimulus Probability. Psychophysiology 22, 530–534. https://doi.org/10.1111/j.1469-8986.1985.tb01645.x

Raisig, S., Welke, T., Hagendorf, H., van der Meer, E., 2010. I spy with my little eye: Detection of temporal violations in event sequences and the pupillary response. Int. J. Psychophysiol. 76, 1–8. https://doi.org/10.1016/j.ijpsycho.2010.01.006

Rajkowski, J., Kubiak, P., Aston-Jones, G., 1994. Locus coeruleus activity in monkey: phasic and tonic changes are associated with altered vigilance. Brain Res. Bull. 35, 607–616.

Rajkowski, J., Kubiak, P., Aston-Jones, G., 1993. Correlations between locus coeruleus (LC) neural activity, pupil diameter and behavior in monkey support a role of LC in attention. Soc. Neurosci. Abstr., 1993 874.

Rajkowski, J., Majczynski, H., Clayton, E., Aston-Jones, G., 2004. Activation of Monkey Locus Coeruleus Neurons Varies With Difficulty and Performance in a Target Detection Task. J. Neurophysiol. 92, 361–371. https://doi.org/10.1152/jn.00673.2003

Ramos, B.P., Arnsten, A.F.T., 2007. Adrenergic Pharmacology and Cognition: Focus on the Prefrontal Cortex. Pharmacol. Ther. 113, 523–536. https://doi.org/10.1016/j.pharmthera.2006.11.006

Ranganath, C., DeGutis, J., D'Esposito, M., 2004. Category-specific modulation of inferior temporal activity during working memory encoding and maintenance. Cogn. Brain Res. 20, 37–45. https://doi.org/10.1016/j.cogbrainres.2003.11.017

Rao, R.P.N., 2005. Bayesian inference and attentional modulation in the visual cortex. Neuroreport 16, 1843–1848.

Rao, R.P.N., Ballard, D.H., 1999. Predictive coding in the visual cortex: a functional interpretation of some extra-classical receptive-field effects. Nat. Neurosci. 2, nn0199_79. https://doi.org/10.1038/4580

Reber, A.S., 1967. Implicit learning of artificial grammars. J. Verbal Learn. Verbal Behav. 6, 855–863. https://doi.org/10.1016/S0022-5371(67)80149-X

Redington, M., Chater, N., 1997. Probabilistic and distributional approaches to language acquisition. Trends Cogn. Sci. 1, 273–281. https://doi.org/10.1016/S1364-6613(97)01081-4

Reimer, J., McGinley, M.J., Liu, Y., Rodenkirch, C., Wang, Q., McCormick, D.A., Tolias, A.S., 2016. Pupil fluctuations track rapid changes in adrenergic and cholinergic activity in cortex. Nat. Commun. 7, 13289. https://doi.org/10.1038/ncomms13289

Robbins, T.W., Everitt, B.J., 1995. Arousal systems and attention., in: The Cognitive Neurosciences. The MIT Press, Cambridge, MA, US, pp. 703–720.

Rolfs, M., Kliegl, R., Engbert, R., 2008. Toward a model of microsaccade generation: The case of microsaccadic inhibition. J. Vis. 8, 5–5. https://doi.org/10.1167/8.11.5

Rommelfanger, K.S., Weinshenker, D., 2007. Norepinephrine: The redheaded stepchild of Parkinson's disease. Biochem. Pharmacol. 74, 177–190. https://doi.org/10.1016/j.bcp.2007.01.036

Rosburg, T., 2004. Effects of tone repetition on auditory evoked neuromagnetic fields. Clin. Neurophysiol. 115, 898–905. https://doi.org/10.1016/j.clinph.2003.11.011

Saarinen, J., Paavilainen, P., Schöger, E., Tervaniemi, M., Näätänen, R., 1992. Representation of abstract attributes of auditory stimuli in the human brain. Neuroreport 3, 1149–1151.

Saffran, J., Hauser, M., Seibel, R., Kapfhamer, J., Tsao, F., Cushman, F., 2008. Grammatical pattern learning by human infants and cotton-top tamarin monkeys. Cognition 107, 479–500. https://doi.org/10.1016/j.cognition.2007.10.010

Saffran, J.R., 2003. Musical Learning and Language Development. Ann. N. Y. Acad. Sci. 999, 397–401. https://doi.org/10.1196/annals.1284.050

Saffran, J.R., Aslin, R.N., Newport, E.L., 1996. Statistical learning by 8-month-old infants. Science 274, 1926–1928.

Saffran, J.R., Johnson, E.K., Aslin, R.N., Newport, E.L., 1999. Statistical learning of tone sequences by human infants and adults. Cognition 70, 27–52. https://doi.org/10.1016/S0010-0277(98)00075-4

Saffran, J.R., Kirkham, N.Z., 2018. Infant Statistical Learning. Annu. Rev. Psychol. 69, 181–203. https://doi.org/10.1146/annurev-psych-122216-011805

Sallinen, M., Kaartinen, J., Lyytinen, H., 1994. Is the appearance of mismatch negativity during stage 2 sleep related to the elicitation of K-complex? Electroencephalogr. Clin. Neurophysiol. 91, 140–148. https://doi.org/10.1016/0013-4694(94)90035-3

Sams, M., Paavilainen, P., Alho, K., Näätänen, R., 1985. Auditory frequency discrimination and event-related potentials. Electroencephalogr. Clin. Neurophysiol. 62, 437–448.

Samuels, E.R., Szabadi, E., 2008a. Functional Neuroanatomy of the Noradrenergic Locus Coeruleus: Its Roles in the Regulation of Arousal and Autonomic Function Part II: Physiological and Pharmacological Manipulations and Pathological Alterations of Locus Coeruleus Activity in Humans. Curr. Neuropharmacol. 6, 254–285. https://doi.org/10.2174/157015908785777193

Samuels, E.R., Szabadi, E., 2008b. Functional Neuroanatomy of the Noradrenergic Locus Coeruleus: Its Roles in the Regulation of Arousal and Autonomic Function Part I: Principles of Functional Organisation. Curr. Neuropharmacol. 6, 235–253. https://doi.org/10.2174/157015908785777229

Sara, S.J., 2009. The locus coeruleus and noradrenergic modulation of cognition. Nat. Rev. Neurosci. 10, 211–223. https://doi.org/10.1038/nrn2573

Sara, S.J., 1985. The locus coeruleus and cognitive function: Attempts to relate noradrenergic enhancement of signal/noise in the brain to behavior. Physiol. Psychol. 13, 151–162. https://doi.org/10.3758/BF03326515

Sara, S.J., Bouret, S., 2012. Orienting and Reorienting: The Locus Coeruleus Mediates Cognition through Arousal. Neuron 76, 130–141. https://doi.org/10.1016/j.neuron.2012.09.011

Sara, S.J., Segal, M., 1991. Chapter 40 - Plasticity of sensory responses of locus coeruleus neurons in the behaving rat: implications for cognition, in: Barnes, C.D., Pompeiano, O. (Eds.), Progress in Brain Research, Neurobiology of the Locus Coeruleus. Elsevier, pp. 571–585. https://doi.org/10.1016/S0079-6123(08)63835-2

Sara, S.J., Vankov, A., Hervé, A., 1994. Locus coeruleus-evoked responses in behaving rats: A clue to the role of noradrenaline in memory. Brain Res. Bull. 35, 457–465. https://doi.org/10.1016/0361-9230(94)90159-7

Sarter, M., Bruno, J.P., 1997. Cognitive functions of cortical acetylcholine: toward a unifying hypothesis. Brain Res. Rev. 23, 28–46. https://doi.org/10.1016/S0165-0173(96)00009-4

Satterthwaite, T.D., Green, L., Myerson, J., Parker, J., Ramaratnam, M., Buckner, R.L., 2007. Dissociable but inter-related systems of cognitive control and reward during decision making: Evidence from pupillometry and event-related fMRI. NeuroImage 37, 1017–1031. https://doi.org/10.1016/j.neuroimage.2007.04.066

Schröger, E., Bendixen, A., Denham, S.L., Mill, R.W., Bőhm, T.M., Winkler, I., 2014. Predictive Regularity Representations in Violation Detection and Auditory Stream Segregation: From Conceptual to Computational Models. Brain Topogr. 27, 565–577. https://doi.org/10.1007/s10548-013-0334-6

Schröger, E., Bendixen, A., Trujillo-Barreto, N.J., Roeber, U., 2007. Processing of Abstract Rule Violations in Audition. PLoS ONE 2, e1131. https://doi.org/10.1371/journal.pone.0001131

Segal, M., Bloom, F.E., 1976. The action of norepinephrine in the rat hippocampus. IV. The effects of locus coeruleus stimulation on evoked hippocampal unit activity. Brain Res. 107, 513–525. https://doi.org/10.1016/0006-8993(76)90141-4

Servan-Schreiber, D., Printz, H., Cohen, J.D., 1990. A network model of catecholamine effects: gain, signal-to-noise ratio, and behavior. Science 249, 892–895. https://doi.org/10.1126/science.2392679

Seu, E., Lang, A., Rivera, R.J., Jentsch, J.D., 2009. Inhibition of the norepinephrine transporter improves behavioral flexibility in rats and monkeys. Psychopharmacology (Berl.) 202, 505–519. https://doi.org/10.1007/s00213-008-1250-4

Shelton, J., Nishino, S., Vaught, J., Dement, W.C., Mignot, E., 1995. Comparative Effects of Modafinil and Amphetamine on Daytime Sleepiness and Cataplexy of Narcoleptic Dogs. Sleep 18, 817–826. https://doi.org/10.1093/sleep/18.10.817

Shi, Y.Q., Sun, H., 2017. Image and Video Compression for Multimedia Engineering: Fundamentals, Algorithms, and Standards, Second Edition. CRC Press.

Siegle, G.J., Steinhauer, S.R., Thase, M.E., 2004. Pupillary assessment and computational modeling of the Stroop task in depression. Int. J. Psychophysiol., Pupillometric Measures of Cognitive and Emotional Processes 52, 63–76. https://doi.org/10.1016/j.ijpsycho.2003.12.010

Simons, D.J., Rensink, R.A., 2005. Change blindness: past, present, and future. Trends Cogn. Sci. 9, 16–20. https://doi.org/10.1016/j.tics.2004.11.006

Sirois, S., Brisson, J., 2014. Pupillometry. Wiley Interdiscip. Rev. Cogn. Sci. 5, 679–692. https://doi.org/10.1002/wcs.1323

Sohoglu, E., Chait, M., 2016. Detecting and representing predictable structure during auditory scene analysis. eLife 5, e19113. https://doi.org/10.7554/eLife.19113

Sokolov, E.N., 1963. Higher Nervous Functions: The Orienting Reflex. Annu. Rev. Physiol. 25, 545–580. https://doi.org/10.1146/annurev.ph.25.030163.002553

Song, A.H., Kucyi, A., Napadow, V., Brown, E.N., Loggia, M.L., Akeju, O., 2017. Pharmacological Modulation of Noradrenergic Arousal Circuitry Disrupts Functional Connectivity of the Locus Ceruleus in Humans. J. Neurosci. 37, 6938–6945. https://doi.org/10.1523/JNEUROSCI.0446-17.2017

Southwell, R., Baumann, A., Gal, C., Barascud, N., Friston, K., Chait, M., 2017. Is predictability salient? A study of attentional capture by auditory patterns. Phil Trans R Soc B 372, 20160105. https://doi.org/10.1098/rstb.2016.0105

SR research, 2010. EyeLink 1000 User Manual, 1.5.0. ed.

Srinivasan, R., 2005. High-resolution EEG: theory and practice, in: Event-Related Potentials: A Methods Handbook. MIT Press, pp. 167–188.

Steere, J.C., Arnsten, A.F.T., 1997. The α-2A noradrenergic receptor agonist guanfacine improves visual object discrimination reversal performance in aged rhesus monkeys. Behav. Neurosci. 111, 883.

Steiner, G.Z., Barry, R.J., 2011. Pupillary responses and event-related potentials as indices of the orienting reflex. Psychophysiology 48, 1648–1655. https://doi.org/10.1111/j.1469-8986.2011.01271.x

Steinhauer, S., Zubin, J., 1982. Vulnerability to schizophrenia: Information processing in the pupil and event-related potential. Biol. Markers Psychiatry Neurol. 371–385.

Steinhauer, S.R., Hakerem, G., 1992. The Pupillary Response in Cognitive Psychophysiology and Schizophreniaa. Ann. N. Y. Acad. Sci. 658, 182–204. https://doi.org/10.1111/j.1749-6632.1992.tb22845.x

Steinhauer, S.R., Siegle, G.J., Condray, R., Pless, M., 2004. Sympathetic and parasympathetic innervation of pupillary dilation during sustained processing. Int. J. Psychophysiol., Pupillometric Measures of Cognitive and Emotional Processes 52, 77–86. https://doi.org/10.1016/j.ijpsycho.2003.12.005

Stelmack, R.M., Siddle, D.A.T., 1982. Pupillary Dilation as an Index of the Orienting Reflex. Psychophysiology 19, 706–708. https://doi.org/10.1111/j.1469-8986.1982.tb02529.x

Stothart, C., Mitchum, A., Yehnert, C., 2015. The attentional cost of receiving a cell phone notification. J. Exp. Psychol. Hum. Percept. Perform. 41, 893–897. https://doi.org/10.1037/xhp0000100

Summerfield, C., de Lange, F.P., 2014. Expectation in perceptual decision making: neural and computational mechanisms. Nat. Rev. Neurosci. 15, 745–756. https://doi.org/10.1038/nrn3838

Summerfield, C., Egner, T., 2016. Feature-Based Attention and Feature-Based Expectation. Trends Cogn. Sci. 20, 401–404. https://doi.org/10.1016/j.tics.2016.03.008

Szabadi, E., 2012. Modulation of physiological reflexes by pain: role of the locus coeruleus. Front. Integr. Neurosci. 6. https://doi.org/10.3389/fnint.2012.00094

Tse, W.S., Bond, A.J., 2002. Difference in serotonergic and noradrenergic regulation of human social behaviours. Psychopharmacology (Berl.) 159, 216–221. https://doi.org/10.1007/s00213-001-0926-9

Turk-Browne, N.B., Isola, P.J., Scholl, B.J., Treat, T.A., 2008. Multidimensional visual statistical learning. J. Exp. Psychol. Learn. Mem. Cogn. 34, 399–407. https://doi.org/10.1037/0278-7393.34.2.399

Turk-Browne, N.B., Jungé, J., Scholl, B.J., 2005. The automaticity of visual statistical learning. J. Exp. Psychol. Gen. 134, 552–564. https://doi.org/10.1037/0096-3445.134.4.552

Turk-Browne, N.B., Scholl, B.J., Chun, M.M., Johnson, M.K., 2009. Neural Evidence of Statistical Learning: Efficient Detection of Visual Regularities Without Awareness. J. Cogn. Neurosci. 21, 1934–1945. https://doi.org/10.1162/jocn.2009.21131

Turk-Browne, N.B., Scholl, B.J., Johnson, M.K., Chun, M.M., 2010. Implicit perceptual anticipation triggered by statistical learning. J. Neurosci. Off. J. Soc. Neurosci. 30, 11177–11187. https://doi.org/10.1523/JNEUROSCI.0858-10.2010

Turner, R., Sahani, M., 2008. Modeling natural sounds with modulation cascade processes, in: Advances in Neural Information Processing Systems. pp. 1545–1552.

Usher, M., Cohen, J.D., Servan-Schreiber, D., Rajkowski, J., Aston-Jones, G., 1999. The Role of Locus Coeruleus in the Regulation of Cognitive Performance. Science 283, 549–554. https://doi.org/10.1126/science.283.5401.549

Vankov, A., Hervé-Minvielle, A., Sara, S.J., 1995. Response to Novelty and its Rapid Habituation in Locus Coeruleus Neurons of the Freely Exploring Rat. Eur. J. Neurosci. 7, 1180–1187. https://doi.org/10.1111/j.1460-9568.1995.tb01108.x

Verleger, R., Heide, W., Butt, C., Kömpf, D., 1994. Reduction of P3b in patients with temporo-parietal lesions. Cogn. Brain Res. 2, 103–116. https://doi.org/10.1016/0926-6410(94)90007-8

Voytko, M.L., Olton, D.S., Richardson, R.T., Gorman, L.K., Tobin, J.R., Price, D.L., 1994. Basal forebrain lesions in monkeys disrupt attention but not learning and memory. J. Neurosci. 14, 167–186.

Wacongne, C., Changeux, J.-P., Dehaene, S., 2012. A Neuronal Model of Predictive Coding Accounting for the Mismatch Negativity. J. Neurosci. 32, 3665–3678. https://doi.org/10.1523/JNEUROSCI.5003-11.2012

Wade, N.J., Tatler, B.W., 2011. Origins and applications of eye movement research. https://doi.org/10.1093/oxfordhb/9780199539789.013.0002

Wang, C.-A., Boehnke, S.E., Itti, L., Munoz, D.P., 2014. Transient Pupil Response Is Modulated by Contrast-Based Saliency. J. Neurosci. 34, 408–417. https://doi.org/10.1523/JNEUROSCI.3550-13.2014

Wang, C.-A., Boehnke, S.E., White, B.J., Munoz, D.P., 2012. Microstimulation of the Monkey Superior Colliculus Induces Pupil Dilation Without Evoking Saccades. J. Neurosci. 32, 3629–3636. https://doi.org/10.1523/JNEUROSCI.5512-11.2012

Wang, C.-A., Munoz, D.P., 2014. Modulation of stimulus contrast on the human pupil orienting response. Eur. J. Neurosci. 40, 2822–2832. https://doi.org/10.1111/ejn.12641

Warren, B.M., Ackroff, J.M., 1976. Two types of auditory sequence perception. Percept. Psychophys. 20, 387–394. https://doi.org/10.3758/BF03199420

Warren, R.M., 2008. Auditory Perception: An Analysis and Synthesis. Cambridge University Press, Cambridge.

Warren, R.M., Gardner, D.A., Brubaker, B.S., James A. Bashford, 1991. Melodic and Nonmelodic Sequences of Tones: Effects of Duration on Perception. Music Percept. Interdiscip. J. 8, 277–289. https://doi.org/10.2307/40285503

Warren, R.M., Obusek, C.J., 1972. Identification of temporal order within auditory sequences. Percept. Psychophys. 12, 86–90. https://doi.org/10.3758/BF03212848

Waterhouse, B.D., Woodward, D.J., 1980. Interaction of norepinephrine with cerebrocortical activity evoked by stimulation of somatosensory afferent pathways in the rat. Exp. Neurol. 67, 11–34. https://doi.org/10.1016/0014-4886(80)90159-4

Weinshenker, D., 2008. Functional consequences of locus coeruleus degeneration in Alzheimer's disease. Curr. Alzheimer Res. 5, 342–345.

Wetzel, N., Buttelmann, D., Schieler, A., Widmann, A., 2016. Infant and adult pupil dilation in response to unexpected sounds. Dev. Psychobiol. 58, 382–392. https://doi.org/10.1002/dev.21377

Whitehouse, P.J., Price, D.L., Struble, R.G., Clark, A.W., Coyle, J.T., DeLong, M.R., 1982. Alzheimer's Disease and Senile Dementia: Loss of Neurons in the Basal Forebrain. Science 215, 1237–1239.

Widmann, A., Schröger, E., Wetzel, N., 2018. Emotion lies in the eye of the listener: emotional arousal to novel sounds is reflected in the sympathetic contribution to the pupil dilation response and the P3. https://doi.org/10.1101/250084

Wierda, S.M., van Rijn, H., Taatgen, N.A., Martens, S., 2012. Pupil dilation deconvolution reveals the dynamics of attention at high temporal resolution. Proc. Natl. Acad. Sci. U. S. A. 109, 8456–8460. https://doi.org/10.1073/pnas.1201858109

Wilson, B., Slater, H., Kikuchi, Y., Milne, A.E., Marslen-Wilson, W.D., Smith, K., Petkov, C.I., 2013. Auditory Artificial Grammar Learning in Macaque and Marmoset Monkeys. J. Neurosci. 33, 18825–18835. https://doi.org/10.1523/JNEUROSCI.2414-13.2013

Winkler, I., 2007. Interpreting the Mismatch Negativity. J. Psychophysiol. 21, 147–163. https://doi.org/10.1027/0269-8803.21.34.147

Winkler, I., Denham, S.L., Nelken, I., 2009. Modeling the auditory scene: predictive regularity representations and perceptual objects. Trends Cogn. Sci. 13, 532–540. https://doi.org/10.1016/j.tics.2009.09.003

Winkler, I., Paavilainen, P., Alho, K., Reinikainen, K., Sams, M., Naatanen, R., 1990. The Effect of Small Variation of the Frequent Auditory Stimulus on the Event-Related Brain Potential to the Infrequent Stimulus. Psychophysiology 27, 228–235. https://doi.org/10.1111/j.1469-8986.1990.tb00374.x

Witte, E.A., Davidson, M.C., Marrocco, R.T., 1997. Effects of altering brain cholinergic activity on covert orienting of attention: comparison of monkey and human performance. Psychopharmacology (Berl.) 132, 324–334. https://doi.org/10.1007/s002130050352

Wolff, C., Schröger, E., 2001. Activation of the auditory pre-attentive change detection system by tone repetitions with fast stimulation rate. Cogn. Brain Res. 10, 323–327. https://doi.org/10.1016/S0926-6410(00)00043-4

Woodward, D.J., Moises, H.C., Waterhouse, B.D., Hoffer, B.J., Freedman, R., 1979. Modulatory actions of norepinephrine in the central nervous system. Fed. Proc. 38, 2109–2116.

Yabe, H., Tervaniemi, M., Reinikainen, K., Näätänen, R., 1997. Temporal window of integration revealed by Mmn to sound omission. Neuroreport 8, 1971–1974.

Yantis, S., Jonides, J., 1984. Abrupt visual onsets and selective attention: evidence from visual search. J. Exp. Psychol. Hum. Percept. Perform. 10, 601–621.

Yellin, D., Berkovich-Ohana, A., Malach, R., 2015. Coupling between pupil fluctuations and resting-state fMRI uncovers a slow build-up of antagonistic responses in the human cortex. NeuroImage 106, 414–427. https://doi.org/10.1016/j.neuroimage.2014.11.034

Yerkes, R., Dodson, J., 1908. The relation of strength of stimulus to rapidity of habit-formation. J. Comp. Neurol.

Yu, A.J., Dayan, P., 2005. Uncertainty, Neuromodulation, and Attention. Neuron 46, 681–692. https://doi.org/10.1016/j.neuron.2005.04.026

Yuille, A., Kersten, D., 2006. Vision as Bayesian inference: analysis by synthesis? Trends Cogn. Sci., Special issue: Probabilistic models of cognition 10, 301–308. https://doi.org/10.1016/j.tics.2006.05.002

Zaborszky, L., Csordas, A., Mosca, K., Kim, J., Gielow, M.R., Vadasz, C., Nadasdy, Z., 2015. Neurons in the Basal Forebrain Project to the Cortex in a Complex Topographic Organization that Reflects Corticocortical Connectivity Patterns: An Experimental Study Based on Retrograde Tracing and 3D Reconstruction. Cereb. Cortex N. Y. NY 25, 118–137. https://doi.org/10.1093/cercor/bht210

Zarow, C., Sitzer, T.E., Chui, H.C., 2008. Understanding hippocampal sclerosis in the elderly: epidemiology, characterization, and diagnostic issues. Curr. Neurol. Neurosci. Rep. 8, 363–370.

Zatorre, R.J., Evans, A.C., Meyer, E., 1994. Neural mechanisms underlying melodic perception and memory for pitch. J. Neurosci. 14, 1908–1919.

Zekveld, A.A., Heslenfeld, D.J., Johnsrude, I.S., Versfeld, N.J., Kramer, S.E., 2014. The eye as a window to the listening brain: Neural correlates of pupil size as a measure of cognitive listening load. NeuroImage 101, 76–86. https://doi.org/10.1016/j.neuroimage.2014.06.069

Zekveld, A.A., Kramer, S.E., Festen, J.M., 2010. Pupil Response as an Indication of Effortful Listening: The Influence of Sentence Intelligibility. Ear Hear. 31, 480. https://doi.org/10.1097/AUD.0b013e3181d4f251

Zerbe, R.L., Rowe, H., Enas, G.G., Wong, D., Farid, N., Lemberger, L., 1985. Clinical pharmacology of tomoxetine, a potential antidepressant. J. Pharmacol. Exp. Ther. 232, 139–143.

Zhao, J., Al-Aidroos, N., Turk-Browne, N.B., 2013. Attention Is Spontaneously Biased Toward Regularities. Psychol. Sci. 24, 667–677. https://doi.org/10.1177/0956797612460407